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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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MEMORANDUM

October 27, 2011

SUBJECT: **Difenoconazole** Human Health Risk Assessment for Amended Section 3 Registration to Add Seed Treatment Use on Oats and Rye and Establish Tolerances in/on Oat Commodities, Rye Commodities, and Wheat Hay.

PC Code: 128847
Decision No.: 440121
Petition No.: 0F7785

Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: 391395
Registration No.: 100-740
Regulatory Action: Section 3 Registration
Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

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This document provides the Health Effects Division's (HED's) risk assessment of requested new use of difenoconazole as a seed treatment on oats and rye.

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1.0 EXECUTIVE SUMMARY

This assessment provides information to support an amended Section 3 registration for the use of difenoconazole as a seed treatment on oats and rye and, in addition, establish a tolerance in/on wheat hay. This document assesses dietary and drinking water risks associated with exposures resulting from currently registered and proposed new uses of and tolerances for difenoconazole. It also assesses potential enhanced sensitivity of infants and children from dietary and/or residential exposure as required under the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Difenoconazole is a broad spectrum fungicide belonging to the triazole group of fungicides. It is currently registered in the U.S. for use as a seed treatment on barley, canola, cotton, sweet corn, wheat, and triticale and for foliar application to numerous food crops and ornamentals. Tolerances for difenoconazole, currently established under 40 CFR §180.475, range from 0.01-35 ppm. Difenoconazole acts by blocking demethylation during sterol biosysnthesis which, in turn, disrupts membrane synthesis. Difenoconazole is available as liquid emulsifiable concentrate, soluble concentrate, emulsion, and ready-to-use formulations. As a seed treatment, it is applied with commercial grade seed treatment equipment. Difenoconazole is applied to field and vegetable crops, landscape ornamentals and golf course turf by commercial applicators using aerial and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand held sprayers.

Proposed New Uses

Syngenta is requesting an amended registration for Dividend® Fungicide (EPA Reg. No. 100-740) to add use as a seed treatment on oats and rye at 11 g ai/100 lb seed, the same maximum use rate it is currently registered for on barley, wheat, and triticale. The petitioner has submitted a Section B reflecting proposed use rates for the 3.1 lb/gal FS formulation (Dividend® Fungicide; EPA Reg. No. 100-740) on oats and rye without any additional restrictive language; supporting draft labeling (dated 9/20/10) was also submitted. Consistent with the currently registered grazing restrictions for green wheat and triticale forage, the proposed label restricts the grazing of green oats and rye forage until 55 days after planting.

[Note: The first food use of difenoconazole, reviewed under PP#2E4051 (DP#s 172067 and 178394, 10/26/92, R. Lascola), was for the establishment of import tolerances in/on barley, rye, and wheat resulting from seed treatment uses of difenoconazole on rye and wheat at 27.2 g ai/100 lb seed and on barley at 10.2 g ai/100 lb seed and that these higher non-domestic maximum use rates were also considered for tolerance setting and risk assessment (food only).]

Hazard Identification

Subchronic and chronic toxicity studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver. Acute and subchronic neurotoxicity studies showed evidence of neurotoxic effects. However, the observed

effects were transient and dose-response was well characterized with identified dose levels at which no observed adverse effect were seen. There are no indications of immunotoxicity in the available studies. No evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice as induction of liver tumors at doses which were considered to be excessively high for carcinogenicity testing. Difenoconazole has been classified as "Suggestive Evidence of Carcinogenic Potential" with risk quantified using a non-linear (Margin of Exposure) approach. The cancer classification is based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. The FQPA Safety Factor is reduced to 1X. Difenoconazole exhibits low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicological database for difenoconazole is sufficient to conduct this risk assessment. However, in accordance with Part 158 Toxicology Data requirements, an immunotoxicity study (870.7800) is required for difenoconazole.

Dose Response Assessment

Toxicological points of departure (PODs) were selected for dietary and drinking water exposures for the assessment of proposed new uses of difenoconazole. Acute and chronic PODs were selected for assessment of food and water exposures. An acute POD for all populations was selected from an acute neurotoxicity study in rats based on reduced grip strength. A chronic POD was selected from a chronic/carcinogenicity study in rats based on body weight effects. Short and intermediate-term incidental oral, dermal and inhalation PODs were selected from an oral rat reproduction study based on decreased body weight effects in pups and parental animals. A dermal absorption factor is applied when dermal exposure endpoints are selected from oral toxicity studies. A dermal absorption factor of 6% was used for the dermal exposure assessment. Inhalation toxicity is assumed to be equivalent to oral toxicity. An uncertainty factor of 100X was applied endpoints selected for all exposures routes (10X for interspecies extrapolation, 10X for intraspecies variation).

Exposure/Risk Assessment and Risk Characterization

Risk assessments were conducted for dietary (food and water) and aggregate exposure for the proposed new uses of difenoconazole as a seed treatment on oats and rye. A new risk assessment for occupational exposures is not required for the proposed new use because occupational risks for existing uses with the same use patterns (application methods and rates) have been previously assessed and do not present risks of concern. A new residential assessment is not required because the proposed new use does not include residential applications or exposures. Screening level acute and refined chronic dietary and drinking water risk assessments indicate that for all commodities, dietary and drinking water exposure estimates are below HED's level of concern. Risk estimates for worker and residential handler and post-application exposure scenarios exposures are not of concern at maximum use rates for existing and proposed new uses. Aggregate risks are not of concern.

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix D have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

2.0 HED RECOMMENDATIONS

2.1 Data Deficiencies/Conditions of Registration

Submission of a revised Section B and a revised Section F are required (see Section 2.2.3). An immunotoxicity study (870.7800) is required for difenoconazole as part of new data requirements under 40 CFR Part 158.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method, GC/NPD method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, LC/MS/MS method REM 147.07b, is available for the determination of residues of difenoconazole and CGA-205375 in livestock commodities. Adequate confirmatory methods are also available.

2.2.2 International Harmonization

Codex maximum residue limits (MRLs) for residues of difenoconazole have been established. However, since no Codex MRLs have been established for residues of difenoconazole in/on oat commodities, rye commodities, and wheat hay. harmonization with Codex is not an issue. Canadian MRLs for residues of difenoconazole have been established at 0.01 ppm for oat grain and 0.01 ppm for rye grain and harmonization with these established Canadian MRLs is recommended. Mexican MRLs for residues of difenoconazole have been established; however, no Mexican MRLs have been established for any of the cereal grain commodities.

2.2.3 Recommended Tolerances

HED has examined the residue chemistry database for difenoconazole and pending submission of a revised Section F (see requirements under Proposed Tolerances), there are no residue chemistry issues that would preclude granting a registration for the requested seed treatment uses of difenoconazole on oats and rye or establishment of tolerances for residues of difenoconazole only in/on the following raw agricultural commodities listed below: Note:

Pregrazing restrictions on forages are not needed for the requested seed treatment uses (See Section 2.2.5)

Oat, grain.....0.01 ppm
Oat, forage.....0.15 ppm
Oat, hay.....0.05 ppm
Oat, straw.....0.05 ppm
Rye, grain.....0.01 ppm
Rye, forage.....0.15 ppm
Rye, straw.....0.05 ppm
Wheat, hay.....0.05 ppm

Note to PM: The recommended tolerance for rye grain (0.01 ppm) should replace the existing tolerance for rye grain (0.1 ppm), which currently applies to imported commodities only. The footnote for rye grain in the existing tolerance should be removed since there will now be US registrations for rye grain.

2.2.4 Revisions to Petitioned-For Tolerances

HED's recommended revisions to the tolerances and/or commodity definitions submitted by Syngenta for this new use petition are listed in Table 1. Tolerances for plant commodities are established under §180.475(a)(1) and are expressed in terms of difenoconazole *per se*. The tolerances proposed by Syngenta are also expressed in terms of difenoconazole *per se* and are listed in Table 1 along with the tolerance levels recommended by HED and corrected commodity definitions.

Table 1. Tolerance Summary for Difenoconazole.

Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	*Correct Commodity Definition;* Comments
Oats, grain	0.1	0.01	*Oat, grain.* The proposed tolerance is too high. Based on the translation and re-evaluation of available barley grain data, no detectable residues of difenoconazole *per se* are expected in/on oat grain from the maximum seed treatment use under consideration. Therefore, the tolerance should be established at the limit of quantitation (LOQ) of the current enforcement method, 0.01 ppm in/on grain; a level consistent with the established Canadian MRL in/on the same commodity.
Oats, forage	0.1	0.15	*Oat, forage.* Based on the translation and re-evaluation of available wheat forage data, and using the OECD MRL calculator, a tolerance of 0.15 ppm is appropriate for the maximum seed treatment use under consideration.
Oats, hay	0.1	0.05	*Oat, hay.* Based on the translation and re-evaluation of available wheat hay data, residues of difenoconazole are not expected to exceed the LOQ of the current enforcement method, 0.05 ppm in/on hay, for the maximum seed treatment use under consideration.

Table 1. Tolerance Summary for Difenoconazole.			
Commodity	**Proposed Tolerance (ppm)**	**Recommended Tolerance (ppm)**	***Correct Commodity Definition;* Comments**
Oats, straw	0.1	0.05	*Oat, straw.* Based on the translation and re-evaluation of available wheat straw data, residues of difenoconazole are not expected to exceed the LOQ of the current enforcement method, 0.05 ppm in/on straw, for the maximum seed treatment use under consideration.
Rye, grain	0.1	0.01	Based on the translation and re-evaluation of available wheat grain data, no detectable residues of difenoconazole *per se* are expected in/on oat grain from the maximum seed treatment use under consideration. Therefore, the tolerance should be established at the limit of quantitation (LOQ) of the current enforcement method, 0.01 ppm in/on grain; consistent with the established Canadian MRL in/on the same commodity. **Note: The recommended tolerance for rye grain (0.01 ppm) should replace the existing import tolerance for rye grain (0.1 ppm).**
Rye, forage	0.1	0.15	See comments above under Oat, forage.
Rye, straw	0.1	0.05	See comments above under Oat, straw.
Wheat, hay	0.1	0.05	Based on the re-evaluation of available wheat hay data, residues of difenoconazole are not expected to exceed the LOQ of the current enforcement method, 0.05 ppm in/on hay, for the maximum seed treatment use under consideration.

2.2.5 Label Recommendations

Pregrazing restrictions are not needed for barley, oat, rye, and wheat forages and should be removed from the proposed and currently registered Dividend® Fungicide (EPA Reg. No. 100-740) labels.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

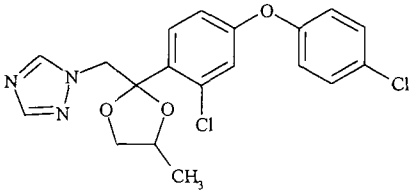
Table 2. Structures and Nomenclature.	
Chemical structure of difenoconazole	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole

Table 2. Structures and Nomenclature.	
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
End-use products (EP)	Dividend® Fungicide, 3.1 lb/gal FS (EPA Reg. No. 100-740).

3.2 Physical/Chemical Characteristics

A detailed description of the physiochemical properties of difenoconazole is provided in Appendix C. Difenoconazole exhibits relatively low solubility in water and higher solubility in solvents. It has a very low vapor pressure. Based on the field and laboratory studies, difenoconazole is persistent in soil and slightly mobile. It has low potential to reach ground water, except in soils of high sand and low organic matter content. Difenoconazole does not present significant concerns for bioaccumulation based on the lipophilicity of the compound, as well as the mammalian metabolism studies.

3.3 Pesticide Use Pattern

There are 28 active difenoconazole registrations, 16 Section 3 uses and 12 Section 18 Emergency Exemptions. Difenoconazole is currently registered in the U.S. for use as a seed treatment on barley, wheat, and triticale, canola, sweet corn and cotton. It is also registered for foliar applications to numerous fruit and vegetable crops, ornamentals and golf course turf. Proposed new uses include seed treatment uses on oats and rye. The use pattern for the proposed new use is provided in Table 3.

Table 3. Maximum Application Rates for Difenoconazole Proposed Uses

Application Site	% AI	Max Single App Rate[1]	Max Seasonal App Rate	Application Method	Reg No.
Seed Treatment – Oats and Rye	32.8	0.0242 lb (11 g) ai/100 lb seed	0.0242 lb (11 g) ai/100 lb seed	commercial treatment	100-740 FC[2]

[1] non-domestic use rates are higher for rye and wheat (27.2 g ai/100 lb seed) [2] SC – Flowable Concentrate

3.4 Anticipated Exposure Pathways

Dietary (food and water) exposures are expected based on proposed uses of difenoconazole as a seed treatment on oats and rye. An occupational exposure assessment for the proposed new use is not required because occupational risks for use of difenoconazole as commercial seed treatment (for barley, wheat and triticale) at the same maximum application rate proposed or oats and rye (11 g ai/100 lb seed) have been previously assessed and do not propose risks of concern. A new residential exposure assessment is not required because there are no residential uses or exposures associated with the proposed new use. The short-term aggregate exposure assessment, which takes into account residential exposure plus average exposure levels to food and water, has been updated to incorporate dietary exposure from the proposed new seed treatment uses.

3.5 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post application are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION/ASSESSMENT

4.1 Toxicology Studies Available for Analysis

The toxicology database for difenoconazole is adequate for evaluating and characterizing difenoconazole toxicity and selecting endpoints for purposes of this risk assessment. With the exception of an immunotoxicity study, all toxicity studies required in accordance with new 40 CFR Part 158 the data requirements have been submitted. An immunotoxicity study (870.7800) is required for difenoconazole. A proposal for difenoconazole immunotoxicity testing regarding dose and species selection to fulfill the 870.7800 guideline requirement has been submitted by the registrant and reviewed by HED (J. Kidwell, 10/20/10, TXR 0055515).

4.2 Absorption, Distribution, Metabolism and Excretion

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats. In one study, the test compound was labeled with C^{14} at either the phenyl or triazole ring. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg of radiolabeled compound or 0.5 mg/kg unlabeled compound by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C]-difenoconazole on day 15. In a second follow-up study [^{14}C]-difenoconazole (phenyl ring label) was administered as single oral gavage dose of 0.5 or 300 mg/kg. The second study was conducted to address deficiencies in the initial study by providing biliary excretion and identification of metabolites.

Difenoconazole was rapidly absorbed and extensively distributed, metabolized, and excreted in rats for all dosing regimens. Distribution, metabolism and elimination of difenoconazole were not sex related in the first study. Recovery of administered dose was 96-108%. Biliary excretion, examined in the second study, constituted the main route of elimination with some dose and sex dependency (75% at the low dose for both sexes; 56% for males and

39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In bile duct cannulated rats, 9-14% of dose was eliminated in the urine at the low dose versus 1% in the high-dose rats. In bile duct cannulated rats, 2-4% was eliminated in the feces at the low dose versus 17-22% at the high dose. Half-lives of elimination are approximately 20 hours for the low dose groups and 33-48 hours for the high dose group. Radioactivity in the blood peaked at 2 to 4 hours at the low and high dose respectively.

Difenoconazole undergoes successive oxidation and conjugation reactions. Following administration of 300 mg/kg of (^{14}C-phenyl) difenoconazole, three major urinary metabolites were identified as CGA 205375 and HO-CGA 205375 (6% of dose), sulfate conjugates (and their isomers) of HO-205375 (3.9% of dose), and the hydroxyacetic metabolite of HO-CGA 205375 (2.0% of dose). No single unknown urinary metabolite accounted for >1.1% of the dose. Free triazole metabolite was detected in the urine of the triazole-label groups and its byproduct was detected in the liver of phenyl labeled groups only.

The study results indicate that difenoconazole and/or its metabolites do not bioaccumulate appreciably following oral exposure since all tissues contained negligible levels (<1%) or radioactivity 7 days post exposure.

A dermal absorption factor of 6% was derived based on data from a triple pack of a 28 rat *in vivo* dermal absorption study and *in vitro* dermal absorption studies conducted with rat and human skin. Inhalation toxicity is assumed to be equivalent to oral toxicity.

4.3 Toxicological Effects

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males and clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. In a subchronic neurotoxicity study in rats, decreased hind limb strength was observed in males only at the mid- and high-doses. However, the effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified no observed adverse effect levels (NOAELs). No systemic toxicity was observed at the limit dose in the most recently submitted 28-day rat dermal toxicity study.

The available toxicity studies indicated no increased susceptibility of rats or rabbits from in utero or postnatal exposure to difenoconazole. In prenatal developmental toxicity studies in rats and rabbits and in the two-generation reproduction study in rats, fetal/offspring toxicity, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

There are no indications in the available studies that organs associated with immune function, such as the thymus and spleen, are affected by difenoconazole. However, a specific immunotoxicity study is not available.

In accordance with HED's current policy and EPA's 2005 Cancer Guidelines,

difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors observed in mice at 300 ppm and higher, the absence of tumors at two lower doses of 10 and 30 ppm, excessive toxicity observed at the two highest doses of 2500 and 4500 ppm, the absence of genotoxic and no evidence of carcinogenicity in rats. HED's Cancer Peer Review Committee recommended use of an MOE approach to risk assessment using the chronic point of departure (POD) based on effects observed in the chronic mouse study relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The POD is considered protective of the cancer effects.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The toxicity profiles for difenoconazole are provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA factor for increased susceptibility to infants and children is reduced to 1x based on the following considerations. Further discussion may be found in the following sections.

- The toxicology data base for difenoconazole is complete and adequate for assessing increased susceptibility under FQPA.
- There is no indication of increased susceptibility of rats or rabbit fetuses to in utero and/or postnatal exposure in the developmental and reproductive toxicity data.
- There are no residual uncertainties in the exposure database.
- The dietary risk assessment is conservative and will not underestimate dietary exposure to difenoconazole.

4.4.1 Completeness of the Toxicology Database

The toxicity database is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. Acceptable acute and subchronic neurotoxicity studies are available. An immunotoxicity study is required under new 40 CFR Part 158 data requirements for registration of a pesticide (food and non-food uses).

4.4.2 Evidence of Neurotoxicity

In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males. Clinical signs of neurotoxicity were observed in females at the limit dose of 2000 mg/kg. The effect in males is considered transient since it was not observed at later observation points. Toxicity in females was observed only at the limit dose. In a subchronic neurotoxicity study in rats decreased hind limb strength was observed in males only. The effects observed in acute and subchronic neurotoxicity studies are transient, and the dose-response is well characterized with identified NOAELs. Based on the toxicity profile, and lack of concern for neurotoxicity, a developmental neurotoxicity study in rats is not required.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The available Agency Guideline studies indicated no increased susceptibility of rats or rabbits to in utero and/or postnatal exposure to difenoconazole. In the prenatal developmental toxicity studies in rats and rabbits and the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In a rat developmental toxicity study developmental effects were observed at doses higher than those which caused maternal toxicity. Developmental effects in the rat included increased incidence ossification of the thoracic vertebrae and hyoid, decreased number of sternal centers of ossification, increased number of ribs and thoracic vertebrae, and decreased number of lumbar vertebrae. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic doses. In the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and will not underestimate dietary exposure to difenoconazole.

4.5 Toxicity Endpoint and Point of Departure

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water), occupational, and residential exposure scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

An acute POD of 25 mg/kg/day (NOAEL) was selected from an acute neurotoxicity study in rats based on reduced fore-limb grip strength in males on day 1 at the LOAEL of 200 mg/kg/day. An uncertainty factor (UF) of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the NOAEL to obtain an acute reference dose (aRfD) of 1.0 mg/kg/day. Since the FQPA factor has been reduced to 1X, the acute population adjusted dose (aPAD) is equivalent to the aRfD. The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

A chronic POD of 0.96 mg/kg/day (NOAEL) was selected from a chronic/oncogenicity oral study in rats based on cumulative decreases in body weight gains in males observed at the LOAEL of 24 mg/kg/day. A UF 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the dose to obtain a chronic reference dose (cRfD/cPAD)

of 0.01 mg/kg/day.

Short-term incidental oral and short- and intermediate term dermal and inhalation PODs of 1.25 mg/kg/day were selected from a two generation reproduction study in rats based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females. Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. An MOE 100 is required for the short- and intermediate-term dermal and inhalation exposure scenarios based on the conventional uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation). There are no residential uses for difenoconazole that would result in incidental oral exposure to children.

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin. Further discussion of the dermal absorption may be found in Attachment A.3.

4.5.2 Recommendations for Combining Exposure Routes

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Oral, dermal and inhalation exposures to residents should be aggregated for difenoconazole because the endpoints selected for these exposure routes are based on common toxicological effects.

4.5.3 Classification of Carcinogenic Potential

Difenoconazole is not mutagenic, and no evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. Liver tumors were observed in mice at 300 ppm and higher; however, based on excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at two lower doses of 10 and 30 ppm, the absence of genotoxic effects, and no evidence of carcinogenicity in rats. In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential," based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. Based on the CPRC recommendation, the risk assessment uses an (MOE) approach utilizing the no-observable-adverse-effects-level (NOAEL) of 30 ppm (4.7 and 5.6 mg/kg/day in males and females, respectively) and the lowest-observable-adverse-effects-level (LOAEL) of 300 ppm (46 and 58 mg/kg/day in males and females, respectively) from the mouse study using only those biological endpoints which were relevant to tumor development (*i.e.*, hepatocellular hypertrophy,

liver necrosis, fatty changes in the liver and bile stasis). The chronic POD of 0.96 mg/kg/day selected based on bodyweight effects is protective of the cancer effects.

4.5.4 Summary of Points of Departure Used in Risk Assessment

Toxicological doses/endpoints selected for the difenoconazole risk assessment are provided in Tables 4 and 5.

Table 4. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (All populations)	NOAEL = 25 mg/kg	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	aRfD = aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study in Rats LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	cRfD = cPAD = 0.01mg/kg/day	Combined chronic toxicity/carcinogenicity (rat; dietary) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains.
Incidental Oral Short-Term (1-30 days)	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X UF_{FQPA} = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies DAF = Dermal Absorption Factor

Table 5. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use Occupational Human Health Risk Assessments				
Exposure Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short- and Intermediate- Term (1-30 days and 1-6 months) DAF = 6%	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF_A = 10X UF_H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F_0 females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

4.6 Endocrine Disruption

As required under FFDCA section 408(p), EPA has developed the Endocrine Disruptor Screening Program (EDSP) to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. This list of chemicals was selected based on the potential for human exposure through pathways such as food and water, residential activity, and certain post-application agricultural scenarios. This list should not be construed as a list of known or likely endocrine disruptors.

Difenoconazole is not among the group of 58 pesticide active ingredients on the initial list to be screened under the EDSP. Under FFDCA sec. 408(p) the Agency must screen all pesticide chemicals. Accordingly, EPA anticipates issuing future EDSP test orders/data call-ins for all pesticide active ingredients.

For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

5.0 DIETARY AND DRINKING WATER EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat, and seed treatment in wheat. HED concludes that the residue of concern for both tolerance enforcement and risk assessment for crops included in this petition is difenoconazole *per se*. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies. The residues of concern for both tolerance setting and risk assessment for livestock commodities are difenoconazole *per se* and its metabolite CGA-205375.

5.1.2 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The CGA-205375 metabolite formed in livestock appears to be formed in the rat also and is, therefore, part of the total toxic exposure for these animals.

5.1.3 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Metabolism Assessment Review Committee (MARC). The residue of concern for plant commodities for tolerance expression and risk assessment purposes is difenoconazole *per se*. The residues of concern in livestock for tolerance setting and risk assessment are difenoconazole and its metabolite CGA 205375. Table 6 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Table 6. Difenoconazole Residues of Concern in Plants and Ruminants.

Matrix		Residues of Concern	
		For Risk Assessment	For Tolerance Expression
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
Drinking Water		Parent Only	NA

Note: The triazole-containing metabolites 1,2,4-T, TA, and TAA should be included in the residues of concern for risk

assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of traizole-derivative fungicides and because of differential toxicity between metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed separately.

5.2 Food Residue Profile

5.2.1 Residues in Crops

No oat and rye field trial data were submitted with the current petition. Instead the petitioner has requested the translation of available wheat and barley field trial data reflecting seed treatment uses of difenoconazole to support the proposed seed treatment uses of difenoconazole on oats and rye. The requested translations are deemed appropriate since the proposed seed treatment uses are substantially similar to those reflected in the available wheat and barley field trial data and the resulting residues were either nondetectable (grain and hay), negligible (straw), or very low (forage) in/on the raw agricultural commodities (RACs) of wheat and barley. Therefore, barley grain data may be translated to oat grain since barley and oat grains are kernels (caryopsis) plus hulls (lemma and palea); wheat grain data may be translated to rye grain since rye and wheat grains are kernels with hulls removed. Wheat forage data may be translated to oat and rye forage. Wheat straw data may be translated to oat and rye straw. Wheat hay may be translated to oat hay.

Based on the re-evaluation of the available wheat and barley field trial data, no detectable residues of difenoconazole (*i.e.*, no residues above the LOQ of the current enforcement method; 0.01 ppm in/on grain and 0.05 ppm in/on hay, straw, and forage), are expected in/on the grain, hay, and straw of oats or in/on the grain and straw of rye from the proposed and/or existing maximum seed treatment use rates of difenoconazole on these grains; tolerances in/on these RACs should be set at the LOQ of the enforcement method. Detectable residues of difenoconazole may be incurred in/on the forages of oats and rye from the proposed and/or existing maximum seed treatment use rates of difenoconazole on these grains; based on the OECD MRL calculator, tolerances of 0.15 ppm in/on these RACs are appropriate.

Previously submitted confined rotational crop data are adequate to support the proposed seed treatment uses of difenoconazole on oats and rye. A 30-day plantback interval is appropriate for the proposed uses on these crops. [Note: Additional confined rotational crop data have been required to support foliar uses of difenoconazole but are not required to support the proposed seed treatment uses. These data have been submitted (MRID 48203402) and are under review in HED (D382946).]

5.2.2 Residue in Livestock and Poultry Residues in Meat, Milk, Poultry, and Eggs

Adequate cattle and poultry feeding studies are available for difenoconazole, and tolerances for difenoconazole residues of concern in livestock commodities were recently reassessed in conjunction with a petition for tolerances in/on carrots, chickpeas, soybeans, stone fruits, strawberries, and turnip greens (PP# 9F7676; DP# 378829, 2/23/11, B. Cropp-Kohlligian). Using the Agency's most recent guidance on constructing reasonably balanced livestock diets (ChemSAC memo, 6/30/08), the maximum dietary burdens (MDB) of livestock for

difenoconazole residues were calculated to be 6.0 ppm for beef cattle, 1.6 ppm for dairy cattle, 0.09 ppm for swine, and 0.11 ppm for poultry. These diets included barley and wheat livestock feedstuffs. Although there are several livestock feedstuffs associated with the proposed uses on oats and rye, HED's review indicates that they will not increase the dietary exposure of livestock to difenoconazole residues and that reassessment of livestock tolerances is not required for this petition.

5.2.3 Residues in Processed Commodities

No new processing data were submitted with the current petition. A wheat processing study is available. These data may be translated to the processed commodities of oats and rye given the nature of the subject wheat processing study which was conducted at an exaggerated rate resulting in nondetectable residues in both the RAC and processed commodities and given the use pattern for these cereal grains. Hence, based on the available wheat processing data, tolerances in the processed commodities of oats and rye are not needed for the seed treatment uses under consideration.

5.3 Water Residue Profile

The drinking water estimates used in the dietary risk assessment were provided by the Environmental Fate and Effects Division. EFED conducted a drinking water assessment for surface water sources using the Pesticide Root Zone/Exposure Analysis Modeling System (PRZM/EXAMS) for the registered and proposed new uses. Groundwater sources were assessed using the Screening Concentration in Groundwater (SCI-GROW v2.3). Among the registered and proposed new uses, the highest estimated drinking water concentrations (EDWCs) for surface water sources were derived for aerial applications of difenoconazole to New York grapes at the maximum annual application rate of 0.46 lb ai/acre. The EDWCs for 1-in-10 year annual peak, 1-in-10 year annual mean, and 36-year annual mean are 15.8, 10.4, and 7.62 µg/L (ppb) respectively. The highest EDWC of difenoconazole from shallow ground water sources is 1.28×10^{-2} µg/L, obtained for the maximum application rate for ornamentals (0.52 lb ai/A). These concentrations can be considered for both the acute and chronic groundwater exposures. The 1-in-10 year annual peak EDWC of 15.8 µg/L (ppb) was used for the acute dietary exposure analysis and the 1-in-10 year annual mean EDWC of 10.4 µg/L (ppb) was used for the chronic dietary exposure analysis.

5.4 Dietary and Drinking Water Exposure and Risk

Screening level acute and refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model with the Food Commodity Intake Database (DEEM-FCID™). Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (i.e., the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the POD divided by the uncertainty factors. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.1 Acute Dietary Risk Assessment

The slightly refined acute analysis for food and water assumed tolerance-level residues, maximum expected residues for wheat grain and barley grain from field trials with a lower method limit of quantitation (LOQ), 100% crop treated (CT), and the available empirical or DEEM™ (ver. 7.81) default processing factors. The resulting acute food exposure estimates were less than HED's level of concern (≤100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population (8 % aPAD) and all population sub-groups; the most highly exposed population subgroup was children1-2 years old with 19 % aPAD.

Table 7. Summary of Acute Dietary Exposure (Food and Drinking Water) and Risk for Difenoconazole at the 95th Percentile.

Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	%aPAD
General U.S. Population	0.25	0.020538	8
All Infants (< 1 year old)		0.039780	16
Children 1-2 years old		**0.047638**	**19**
Children 3-5 years old		0.037050	15
Children 6-12 years old		0.021576	9
Youth 13-19 years old		0.011240	5
Adults 20-49 years old		0.014699	6
Adults 50+ years old		0.019351	8
Females 13-49 years old		0.015084	6

5.4.2 Chronic Dietary Risk Assessment

The somewhat refined chronic analysis for food and water assumed tolerance-level residues for some commodities, average field trial residues for the majority of commodities, the available empirical or DEEM™ (ver. 7.81) default processing factors, and 100 % CT. The resulting chronic food exposure estimates were less than HED's level of concern (<100% of the chronic PAD) for the general U.S. population (17 % cPAD) and all population sub-groups; the most highly exposed population subgroup was children 1-2 years old with 46 % cPAD.

Table 8. Summary of Chronic Dietary (Food and Drinking Water) Exposure and Risk for Difenoconazole.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.01	0.001687	17
All Infants (< 1 year old)		0.003001	30
Children 1-2 years old		**0.004573**	**46**
Children 3-5 years old		0.003607	36
Children 6-12 years old		0.002027	20
Youth 13-19 years old		0.001307	13
Adults 20-49 years old		0.001317	13

Table 8. Summary of Chronic Dietary (Food and Drinking Water) Exposure and Risk for Difenoconazole.			
Population Subgroup	**cPAD (mg/kg/day)**	**Exposure (mg/kg/day)**	**%cPAD**
Adults 50+ years old		0.001562	16
Females 13-49 years old		0.001373	14

The requested amended uses of difenoconazole did not result in an increase in dietary exposure estimates for free triazole or conjugated triazoles. Therefore, the last dietary exposure analyses for the triazole metabolites (D388469, T. Morton, 4/27/11) will not need to be updated.

6.0 RESIDENTIAL EXPOSURE AND RISK

A new residential exposure assessment is not required for the proposed new seed treatment use because there are homeowner uses or application to residential areas associated with the seed treatment use.

6.1 Residential Bystander Postapplication Inhalation Exposure

Based on the Agency's current practices, a quantitative residential bystander postapplication inhalation exposure assessment was not performed for [chemical] at this time. However, volatilization of pesticides may be a potential source of postapplication inhalation exposure to individuals nearby to pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009. The Agency received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate postapplication inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative postapplication inhalation exposure assessment for pyroxasulfone.

6.2 Spray Drift

Spray drift is always a potential source of exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for [chemical]. The Agency has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The Agency has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods.

After the policy is in place, the Agency may impose further refinements in spray drift management practices to reduce off-target drift with specific products with significant risks associated with drift.

7.0 AGGREGATE EXPOSURE AND RISK ASSESSMENT

In accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. In an aggregate assessment, risks from relevant sources are added together and compared to a level of concern. Since a common effect has been identified for assessment of short-term oral, dermal, and inhalation exposures (changes in body weights and body-weight gains) for difenoconazole, the short-term aggregate risk assessment combines exposure from food, water, and residential sources. Only short-term residential exposures are expected based on current use patterns. The acute and chronic exposure estimates from the dietary exposure analyses represent aggregate risk for acute and chronic exposures.

7.1 Short-Term Aggregate Risk to Residential Applicators

Short term aggregate exposure takes into account residential exposure plus average exposure levels to food and water (considered to be a background exposure level). The short term aggregate risk for residential handlers is the estimated risk associated with combined risks from average food and drinking water exposures and dermal and inhalation exposures to adult applicators. Short term aggregate risk estimates for residential handlers are provided in Table 9 aggregates the short-term risk for adults from residential handler exposure and average food and water exposure (as a background). The lowest aggregate MOE is 260, which is greater than the target MOE of 100 and therefore not of concern.

Table 9: Estimated Difenoconazole Short-term Aggregate Risk to Adults from Residential Handler Activities

Exposure Scenario	Target MOE[1]	Route of Exposure	Daily dose	NOAELs	MOE at Day 0	Combined MOE[4]
Average Food and Water (As background)	N/A	Food and water	0.0018	1.25	700 [2]	NA
Hose End Sprayer - Ornamentals	100	Dermal and Inhalation	0.0022		575 [3]	310
Handheld Pump Spray - Ornamentals			0.0031		400	260
Hose End Sprayer – Flower Gardens			0.0019		660	340
Handheld Pump Spray – Flower Gardens			0.0021		590	320

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 0.96
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal and inhalation = [(short -term NOAEL)/(high-end inhalation and dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE handler inhalation and

dermal)].

7.2 Short-Term Aggregate Risk for Residential Post-Application Exposure

Table 10 aggregates the short-term risk for adults from residential post application, and average food and water exposure. The highest post application exposure from residential use on turf was used in the short term aggregate. The aggregate MOE is 600, which is greater than the target MOE of 100. This aggregate exposure assessment is considered very conservative because the assumptions used for each of the scenarios separately are already high end (i.e., time spent outdoors, dislodgeable residues).

Table 10: Estimated Difenoconazole Short-term Aggregate Risk from Residential Post-Application Activities

Exposure Scenario	Target MOE[1]	Route of Exposure	Exposure or Daily dose	NOAELs	MOE at Day 0	Combined MOE[4]
Average Food and Water Adult	N/A	Food and water	0.0018	1.25	700 [2]	NA
Adult Golfer	100	Dermal	0.00024		5200 [3]	600

[1] Target MOE= 100, Developmental rat- increased incidence of rudimentary risks. NOAEL = 30
[2] MOE food and water = [(short-term oral NOAEL)/(chronic dietary exposure)]
[3] MOE dermal = [(short -term dermal NOAEL)/(high-end dermal residential exposure)]
[4] Aggregate Combined MOE (food, water, and residential) = 1÷ [(1÷MOE food and water) + (1÷MOE post appl. dermal)].

8.0 CUMULATIVE RISK

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether difenoconazole has a common mechanism of toxicity with other substances. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to difenoconazole and any other substances and, difenoconazole does not appear to produce a toxic metabolite produced by other substances which have tolerances in the U. S. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that difenoconazole has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/fedrgstr/EPA_PEST/2002/January/Day_16/.

9.0 OCCUPATIONAL EXPOSURE AND RISK

Occupational risks for existing uses with the same use patterns (application methods and

rates) as the proposed new use have been previously assessed (see Section 10.0) and do not present risks of concern. Therefore, a new occupational exposure assessment is not required for the proposed new seed treatment uses.

10.0 REFERENCES

Difenoconazole. Amended Section 3 Registration (Dividend® Fungicide) to Add Seed Treatment Uses on Oats and Rye and Establish Tolerances in/on Oat Commodities, Rye Commodities, and Wheat Hay. Summary of Analytical Chemistry and Residue Data. B. Cropp-Kohlligian, D384073, 10/27/11

Difenoconazole. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Registration Request Seed Treatment Uses on Oats and Rye. T. Morton, D389652, 10/27/11

Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address The Amended Difenoconazole Section 3 Registration to Add Uses on Carrots, Chickpeas, Soybeans, Stone Fruits (Group 12), Strawberries, and Turnip Greens and The Tetraconazole Section 3 Registration to Add Field Corn, Pop Corn, Crop Subgroup 13-07F, and Crop Subgroup 13-07G (except cranberry). T. Morton, D386652, 2/16/11

Difenoconazole: Occupational and Residential Exposure Assessment for the Proposed New Use of Difenoconazole on Proposed New Uses of Difenoconazole on Strawberry, Carrot, Chickpeas, Soybean, Stone Fruit: Group 12 and Golf Course Turfgrass B. Daiss, D371037 2/24/11

Difenoconazole (Parent Only) Drinking Water Assessment in Support of New Use Registration Action for Golf Course Turf. I. Maher, D371044, 6/1/10

Difenoconazole. Request for Restatement of 1994 EPA Cancer Classification and Risk Assessment Approach Using Current Terminology. P.V. Shah, D 318039, 3/1/07

Difenoconazole – with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment, J. Chen, 12/18/08

APPENDICES

A. TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent	Y	Y	42090022 42090021
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	42090013
870.3200	21/28-Day Dermal Toxicity	N	Y	42090013 46950310
870.3250	90-Day Dermal Toxicity	N	N	
870.3465	90-Day Inhalation Toxicity	N	N	
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	42090016 42710008
870.3700b	Prenatal Developmental Toxicity - Non-Rodent	Y	Y	42090017 42710008
870.3800	Reproduction and Fertility Effects	Y	Y	42090018
870.4100a	Chronic (Oral) Toxicity - Rodent	Y	Y	42090015 42710006
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	42090012 42710005
870.4200a	Carcinogenicity - Rat	Y	Y	42090019 42710010
870.4200b	Carcinogenicity - Mouse	Y	Y	42090015 42710006
870.4300	Combined Chronic Toxicity /Carcinogenicity	Y	Y	42090015 42710006
870.6100a	Neurotoxicity - Acute Delayed Neurotox.- Hen	N	N	---
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	---
870.6200a	Neurotoxicity - Acute - Rat	Y	Y	46950327
870.6200b	Neurotoxicity -Subchronic - Rat	Y	Y	46950329
870.6300	Developmental Neurotoxicity	N	N	--
870.7800	Immunotoxicity	Y	N	--

A.2 Toxicity Profiles

Table 1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	**Study Type**	**MRID No.**	**Results**	**Toxicity Category**
870.1100	Acute oral	42090006	LD_{50} = 1450 mg/kg	III
870.1200	Acute dermal	42090007	LD_{50} > 2010 mg/kg	III
870.1300	Acute inhalation	42090008	LC_{50} > 3.3 mg/L	III
870.2400	Eye irritation	42090009	Mild irritation reversible in 7 days	III
870.2500	Dermal irritation	40789807	Slight irritation	IV
870.2600	Skin sensitization	42090011, 42710004	Negative	N/A

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	42090022 (1987) Acceptable/guideline 0, 20, 200, 750, 1500 or 3000 ppm 0, 1, 10, 37.5, 75 and 150 mg/kg/d	NOAEL = 20 ppm (1 mg/kg/day) LOAEL = 200 ppm (10 mg/kg/day) based on the 10% decrease in body weight in the 200 ppm females (as well as a negative trend in feed consumption) and Increases in absolute liver weights in both sexes
870.3100	90-Day oral toxicity (mouse)	42090021 (1987) Minimum/guideline 0, 20, 200, 2500, 7500 or 15,000 ppm M: 0, 2.9, 30.8, 383.6, 1125 and 2250 mg/kg/d F: 0, 4.1, 41.5, 558.9, 1125 and 2250 mg/kg/d	NOAEL = 20 ppm (2.9 mg/kg/day) LOAEL = 200 ppm (30.8 mg/kg/day) based on body weight changes & liver histopathology.
870.3150	26-Week oral toxicity	42090012 (1987) Minimum/ guideline 0, 100, 1000, 3000 or 6000 ppm M: 0, 3.6, 31.3, 96.6 and 157.8 mg/kg/d F: 0, 3.4, 34.8, 110.6 and 203.7 mg/kg/d	NOAEL = 3000 ppm (31.3 mg/kg/day in males/34.8 mg/kg/day in females) LOAEL = 6000 ppm (96.6 mg/kg/day in males/110.6 mg/kg/day in females), based primarily on microscopic examination of CGA 169374-related lenticular cataracts.
870.3200	21/28-Day dermal toxicity (rat)	42090013 (1987) Minimum/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption.
870.3200	21/28-Day dermal toxicity (rat)	46950310 (2000) Acceptable/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL (systemic) = 1000 mg/kg/day LOAEL (systemic) was not determined. NOAEL (dermal) = 100 mg/kg/day LOAEL (dermal) = 1000 mg/kg/day based on hyperkeratosis at the skin application site.
870.3700a	Prenatal developmental in (rat)	42090016, 42710007 (1987) Minimum/ guideline 0, 2, 20, 100 or 200 mg/kg/d from GD 6-15 (nominal doses differed widely from theoretical, this required altering NOAEL/LOAEL values)	Maternal NOAEL = 16 mg/kg/day LOAEL = 85 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 85 mg/kg/day LOAEL = 171 mg/kg/day based on alterations in fetal ossification.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3700b	Prenatal developmental in (rabbit)	42090017, 42710008 (1987) Minimum/ guideline 0, 1, 25 or 75 mg/kg/d from GD 7-19	Maternal NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain and food consumption. Developmental NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on nonsignificant increases in postimplantation loss and resorptions/doe and a significant decrease in fetal weight.
870.3800	Reproduction and fertility effects (rat)	42090018 (1988) Minimum/ guideline 0, 25, 250 or 2500 ppm 0, 1.25, 12.5 and 125 mg/kg/d	Parental/Systemic NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on reductions (statistically nonsignificant) in body weight gain which appear to be part of a dose-related trend days 70-77 prior to mating, days 0-7 of gestation, and days 7-14 of lactation Offspring NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on a significant reduction in the body weight of F1 male pups at day 21 in the 250 ppm group.
870.4100b	Chronic toxicity (dog)	42090012, 42710005 (1988) Minimum/ guideline 0, 20, 100, 500 or 1500 ppm M: 0, 0.71, 3.4, 16.4 and 51.2 mg/kg/d F: 0, 0.63, 3.7, 19.4 and 44.3 mg/kg/d	NOAEL = 100 ppm (3.4 mg/kg/day in males/3.7 mg/kg/day in females) LOAEL = 500 ppm (16.4 mg/kg/day in males/19.4 mg/kg/day in females), based on significant inhibition of body weight gain in females.
870.4200	Carcinogenicity (rat)	42090019, 42710010 (1989) Minimum/ guideline 0, 10, 20, 500 or 2500 ppm M: o, 0.48, 0.96, 24.12 and 123.7 mg/kg/d F: 0, 0.64, 1.27, 32.79 and 169.6 mg/kg/d	NOAEL = 20 ppm (0.96 mg/kg/day in males/1.27 mg/kg/day in females) LOAEL = 500 ppm (24.1 mg/kg/day in males/ 32.8 mg/kg/day in females) based on reductions in cumulative body weight gains in the 500 and 2500 ppm groups. No evidence of carcinogenicity
870.4300	Carcinogenicity (mouse)	42090015, 42710006 (1989) Minimum/ guideline 0, 10, 30, 300, 2500 or 3000 ppm M: 0, 1.51, 4.65, 46.29, 423.1 and 818.9 mg/kg/d F: 0, 1.9, 5.63, 57.79 and 512.6 mg/kg/d	NOAEL = 30 ppm (4.7 mg/kg/day in males/5.6 mg/kg/day in females) LOAEL = 300 ppm (46.3 mg/kg/day in males/57.8 mg/kg/day in females) based on reductions in the cumulative body weight gains and hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis in the 300, 2500 & 4500 ppm groups. Evidence of carcinogenicity (liver adenoma/carcinoma in both sexes)
870.5100	*In vitro* bacterial gene mutation *(Salmonella typhimurium/ E. coli)*/ mammalian activation gene mutation assay	42090019, 42710010 (1989) Minimum/ guideline 340 - 5447 µg/plate; 85 - 1362 µg/plate (repeat assay with TA1537 and TA98)	There were sufficient and valid data to conclude that CGA 169374 technical was negative in the microbial gene mutation assay.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300	*in vitro* mammalian cell gene mutation assay in mouse lymphoma cells	42090024 (1986) Unacceptable/ guideline	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950319 (2001) Acceptable/ guideline 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950321 (2001) Acceptable/ guideline 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background.
870.5375	*In vitro* Mammalian Cytogenetics (chromosomal aberrations) assay in human lymphocytes	46950323 (2001) Acceptable/ guideline 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background.
870.5385	*In vivo* mammalian chromosomal aberration test Assay in Mice	42090023 (1986) Unacceptable/guideline 250, 500 or 1000 mg/kg	There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised.
870.5395	*In vivo* mammalian cytogenetics - erythrocyte micronucleus assay in mice	41710011 (1992) Acceptable/guideline Doses up to 1600 mg/kg	Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-1 69374 (91.2% a.i).
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	4210012 (1992) Acceptable/ guideline Doses up to 50 µg/mL	CGA-i69374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090027 (1985) Unacceptable/ guideline 0.25-31.25 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) primary rat hepatocyte assay conducted with difenoconazole technical at concentrations ranging from 0.25 to 31.25 µg /mL. The sensitivity of the study was severely compromised.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090026 (1985) Unacceptable/ guideline 0.08-10 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) human fibroblast assay conducted with difenoconazole tech. at conc. ranging from 0.08 to 10 µg /mL.
870.6200a	Acute neurotoxicity screening battery	46950327 (2006) Acceptable/ guideline 0, 25, 200 or 2000 mg/kg/d	NOAEL (M) = 25 mg/kg/day LOAEL (M) = 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. NOAEL (F) = 200 mg/kg/day LOAEL (F) = 2000 mg/kg/day based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in and decreased motor activity.
870.6200b	Subchronic neurotoxicity screening battery	46950329 (2006) Acceptable/ guideline 0, 40, 250, or 1500 ppm M; 0, 2.8, 17.3 or 107.0 mg/kg/d F: 0, 3.2, 19.5, or 120.2 mg/kg/d	NOAEL (M) = 40 ppm (2.8 mg/kg/day) LOAEL (M) = 250 ppm (17.3 mg/kg/day) based on decreased hind limb strength. NOAEL (F) = 250 ppm (19.5 mg/kg/day) LOAEL (F) = 1500 (120.2 mg/kg/day) based on decreased body weight, body weight gain and food efficiency.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) Acceptable/ guideline 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Acceptable/ guideline Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA- 169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. [^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

Table 2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Acceptable/ guideline in conjunction with MRIDs 420710013, 42710014 listed below Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	The absorption, distribution, metabolism, and excretion of CGA 169374 were studied in groups of male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C)CGA-169374 on day 15. The test compound was labeled with C^{14} at either the phenyl or triazole ring. **[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all** dosing regimens. the extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours for an dosing group. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days postexposure. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2; B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized. These studies indicate that distribution, metabolism, and elimination of CGA-169374 were not sex related. There was a slight dose difference in the metabolism and elimination of CGA-169374. In phenyl and triazole labeling studies, fecal excretion of radioactivity was higher in the high dose animals compared to the low dose animals, and an additional metabolite was found in the feces of the high dose animals compared to the low dose animals. There was no major difference in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites identified. The studies also showed that administration of 0.5 and 300 mg/kg CGA- 169314 did not induce any treatment related clinical effects.

APPENDIX A.3 HAZARD IDENTIFICATION AND ENDPOINT SELECTION

A.3.1 Acute Population Adjusted Doses (aPAD) – All Populations

Selected Study: Acute Neurotoxicity Study in Rats
MRID 46950327
Dose and Endpoint for Establishing an aPAD: NOAEL is 25 mg/kg/day. LOAEL is 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1.
Uncertainty Factor (UF): 100 This includes 10x for interspecies extrapolation and 10x for intraspecies variation.
Comments about Study/Endpoint: The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

$$\textbf{General Population aPAD} = \frac{\textbf{(NOAEL) 25 mg/kg}}{\textbf{(UF) 100}} = \textbf{0.25 mg/kg}$$

A.3.2 Chronic Population Adjusted Dose (cPAD) – All Populations

Selected Study: Chronic/Oncogenicity Study in Rats
MRID 42090019/20
Dose and Endpoint for Establishing an cPAD: The NOAEL is 0.96 mg/kg/day. The LOAEL is 24.12 mg/kg/day based on cumulative decreases in body weight gains at 24.12 mg/kg/day in males.
Uncertainty Factor (UF): 100 This includes 10X for interspecies extrapolation and 10x for intraspecies variation.

$$\textbf{General Population cPAD} = \frac{\textbf{(NOAEL) 0.96 mg/kg/day}}{\textbf{(UF) 100}} = \textbf{0.01 mg/kg/day}$$

A.3.3 Incidental Oral Exposure (Short-Term)

Selected Study: Two Generation Reproduction Study in Rats
MRID 42090018
Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females.
Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: There are no residential uses for difenoconazole that would

result in incidental oral exposure to children. However, a short term oral exposure endpoint is required for aggregate risk assessment.

A.3.4 Dermal Absorption

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin. The DAF was selected by a special working group of the Antimicrobials Division Toxicity Endpoint Selection Committee (12/18/08 memorandum from J. Chen to M. Swindell – Attachment A.3).

A.3.5 Dermal Exposure (Short and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body weight gain in F0 females.. Dermal absorption is 6%.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. A DAF of 6% is applied to the POD for dermal exposure.

A.3.6 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

See Section A.4.3

A.4 EXECUTIVE SUMMARIES FOR SUPPORTING TOXICITY STUDIES

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat MRID 42090022

CGA-169374 Technical was administered orally in feed admixtures to six groups of rats of both sexes at 0 ppm, 20 ppm, 200 ppm, 750 ppm, 1500 ppm, and 3000 ppm for 13 weeks. The results of this dietary subchronic evaluation of the toxicity of the test article were generally unremarkable. There was a significant trend for decreased body weights in both sexes, and the 200 ppm female rats showed an approximate 10% decrease in body weight relative to their controls concomitant with decreased food consumption. There was one dose—related effect of the chemical discovered during the histopathology examination, that identified modest diffuse hepatocellular enlargement, vis a vis. increased liver weights, in rats of both sexes at the two highest doses tested. Additionally, although not statistically significant, compared to the other groups there was an increase in the frequency and quantity of ketones in the urine of group 6 males. The presence of elevated ketone levels may be due to gluconeogenesis driven by decreased protein intake from the diet as a result of decreased food intake. The somewhat compromised nutritional status of the rats could possibly and indirectly have promoted the hepatocellular enlargement as well.
It is possible to conclude from this study, that based on approximately 10% decrease in body weight in the 200 ppm females (concomitant with a negative trend for food consumption) and increases in absolute liver weights in both sexes appearing at 750 ppm, the LOAEL is 200 ppm. The NOAEL was 20 ppm.
Core Classification: Minimum

870.3100 90-Day Oral Toxicity – Mouse MRID 42090021

CGA 169374 was offered in feed admixtures to five groups of mice composed of 15 animals/group/sex and 20 mice per sex for controls in dietary concentrations of 20 ppm, 200 ppm, 2500 ppm, 7500 ppm, or 15000 ppm for 13 weeks. Most of the mice fed 7500 ppm or 15,000 ppm test article, groups 5 and 6 respectively, died during the first week on study. There were some CGA 169374-related effects. The statistical analysis of total food consumption and body weight changes over the course of the study showed significantly reduced body weight gain for paired group 4 (2500 ppm) females and a significant negative trend. Compound—related effects from histologic examination were confined to the liver. Hepatotoxicity in mice that DOS was evidenced by hepatocellular enlargement and necrosis of individual hepatocytes. Those mice that survived to the end of the study showed hepatotoxicity that included hepatocellular enlargement in group 4 animals and group 3 males and hepatocytic vacuolization in group 4 animals. Furthermore, coagulative necrosis was observed in the livers of 4/9 group 4 females. This finding, however, was not considered treatment related, because the foci were frequently small and random. The animals in groups 5 and 6, which represent the unscheduled deaths, had a high incidence of changes consistent with stress. The changes included lymphoid depletion or necrosis of the spleen, lymph nodes, and thymus, hypocellularity of the femoral marrow, mucosal erosion/ulceration of the glandular stomach, and in the female mice necrosis of individual cells in the adrenal cortex, specifically in the zona reticularis. Hyperkeratosis of the

nonglandular stomach was observed in males especially from group 6. The study director suggests the "stress" effects may be related to inappetence and a failure to eat as opposed to a direct effect of the test article. On the strength of the available data as they relate to the dose levels tested and to the parameters observed, the body weight changes and the liver histopathology form the basis for setting the NOAEL at 20 ppm, and the LOAEL at 200 ppm. The mortality data indicate the MTD was exceeded and is likely S 7500 ppm.

870.3150 26 Week Oral Feeding study –dog OPPTS MRID 42090012

CGA 169374 was offered in feed admixtures to five groups of beagle dogs composed of three animals/group/sex in dietary concentrations of 0 ppm, 100 ppm, 1000 ppm, 3000 ppm, or 6000 ppm for a minimum of 28 weeks. None of the dogs DOS. Compound— related effects, developed essentially at the 3000 ppm and 6000 ppm dose levels. The singularly most striking compound effect was bilateral lenticular cataracts ophthalmoscopically-observed in all dogs at 6000 ppm and in one female beagle at 3000 ppm. Additionally, iridic changes (irregular pupillary margins, miosis), secondary to lens induced uveitis, were also present in the affected animals. There were also reductions in mean body weight in females and males at 6000 ppm test compound throughout the study; weight loss was observed during the first three weeks on study. Body weight loss was precipitated by moderate to severe reductions in mean food consumption in females and males at 6000 ppm during the study with slight reductions observed in males at 3000 ppm and 1000 ppm and in one female at 3000 ppm. Furthermore, there were slight reductions in values for red blood cell count, hemoglobin, and hematocrit in females and males at 6000 ppm. There were also decrements in some serum clinical chemistry measurements including calcium and total protein in females at 6000 ppm and moderate increases in serum alkaline phosphatase in one or both sexes at 3000 ppm. There were modest alterations in several absolute and/or relative organ weight measurements to include the heart, prostate gland, salivary gland, uterus, kidney, liver, and brain at the highest dose tested (HOT). Nevertheless, liver weight measurements were also increased in Group 4 females. There were no other test article—related changes in any other parameter examined. On the strength of the available data as they relate to the dose levels tested and the parameters observed, the LOAEL and the NOAEL for the test article in female and male beagle dogs were 3000 ppm and 1000 ppm, respectively, based primarily on microscopic examination of CGA 169374-related lenticular cataracts. Core Classification: Minimum

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat MRID 42090016

CGA 169347 technical was administered by gavage on days 6-15 of gestation to presumed pregnant rats at 0, 2, 20, 100, or 20a mg/kg. Significant decreases in maternal body weight gain and feed consumption were observed during the dosing period for the feed consumption were observed during the dosing period for the 100 and 200 mg/kg groups. These animals also exhibited a significant increase in the incidence of excess salivation. There was a non significant decrease in the mean number of fetuses per dam, and non significant increases in the mean number of resorptions per dam and % postimplantation loss in the 200 mg/kg group. There was a slight (non significant) decrease in mean fetal body weight at the 200 mg/kg group. The

following represents the significant alterations in the development of fetuses in the 200 mg/kg group. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae in this group. These findings may be related to maternal toxicity. This study may be upgraded after satisfactory review of the response to the noted deficiencies.
core classification: supplementary. NOTE: Due to the relatively high percent deviation of the actual doses tested from the theoretical concentration the effect levels have been modified accordingly. This modification may be subject to change as the purity is currently unknown.
Maternal NOAEL = 16 mg/kg; Maternal LOEL = 85 mg/kg; Developmental Toxicity NOAEL = 85 mg/kg; Developmental Toxicity LOAEL = 171 mg/kg

870.3700b Prenatal Developmental Toxicity Study – Rabbit MRID 42090017

CGA 169347 technical was administered by gavage on days 7—19 ofgestation to presumed pregnant rabbits at 0, 1, 25, or 73 mg/kg. Maternal toxicity was observed in this study as the death of one doe and abortions observed in two other high dose does. In addition, significant reductions in body weight gain of high dose does, were present days 7-10, 10—14, 7-20, and 0—29. These reductions correspond with reduced feed consumption during these intervals (significant reductions in feed consumption in the HDT were only observed during the treatment period, not after treatment). Slight nonsignificant increases in postimplantation loss and resorptions/doe were observed in the HDT. The significant decrease in fetal weight at the HDT may have been due to treatment. The significant differences in fetal weight observed at the low and mid dose were apparently not due to treatment.
Core Classification: supplementary
Maternal NOAEL = 25 mg/kg; Maternal LOEL = 75 mg/kg
Developmental Toxicity NOAEL 25 mg/kg; Developmental Toxicity LOEL = 75 mg/kg

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat MRID 42090018

In a two generation reproduction study, difenoconazole was administered in the diet to male and female rats at 0, 25, 250, or 2500 ppm [0, 1.25, 12.5, or 125 mg/kg/day, respectively]. Statistically significant reductions in body weight gains of F0 and F1 males were observed at 2500 ppm during Days 70-77 and during the course of the study [terminal body weight minus Day 0 body weight]. Significant reductions in body weight gains of F0 and F1 females were seen during the pre-mating, gestation, and lactation periods. A dose-related, but non-statistically significant decreases in body weight gain was seen in F0 females at 250 ppm during Days 70-77 prior to mating, Days 0-7 of gestation, and Days 7-14 of lactation:
At 2500 ppm, significant reductions in pup body weight were detected on Days 0, 4 [pre- and post culling], 7, 14, and 21 for males and females of both generations. There was a significant reduction in the body weight of F1 male pups on Day 21 in the 250 ppm group. The percentage of male pups in the F1 generation surviving Days 0-4 was significantly reduced in the 2500 ppm

group: For parental toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day is based on the decreased maternal body weight gain; the NOAEL is 25 ppm [1.25 mg/kg/day. For offspring toxicity, the LOAEL of 250 ppm [12.5 mg/kg/day] is based on decreased pup weights at Day 21; the NOAEL is 25 ppm [1.25 mg/kg/day].

A.4.4 Chronic Toxicity

870.4100a (870.4300) Combined Chronic Toxicity/Carcinogenicity – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group. Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

870.4100b Chronic Toxicity - Dog MRID 42090012

CGA 169347 was administered in the diet to male and female dogs at 0, 20, 100, 500, or 1500 ppm. The NOAEL was 100 ppm and the LOAEL was
500 ppm based on the following. Females receiving 1500 ppm in the diet had a significant reduction in body weight gain on day 7. Females in the 500 and 1500 ppm groups, although not statistically significant, had inhibited body weight gain throughout the study. These animals also had significant reductions in food consumption on days 7, 35, 70, and 357. The reduction in mean percent reticulocytes at the highest dose tested on day 359 may have been related to treatment, Significant increases (treatment related at day 85; dose—related at days 175 and 359) were observed in alkaline phosphatase in males receiving 1500 ppm. This study may be upgraded upon satisfactory review of the registrants response to the deficiencies (submission of the purity and raw daily observation data).
Classification: core—supplementary

A.4.5 Carcinogenicity

870.4200a Carcinogenicity/Chronic Study – Mice MRIDs 42090015 and 42710006

CD-I mice were fed diets containing difenoconazole at 0; 10; 30; 300; 2500or 4500 [males only] for 78 weeks. The NOAEL was 30 ppm equal to 4.65 mg/kg/d in males and 5.63mg/kg/d in females respectively. The LOAEL was 300 ppm equal to 46.29 mg/kg/d in males and

57.79mg/kg/d in females based on reductions in the cumulative body weight gains at the higher dose levels.

Discussion of Tumor Data: Difenoconazole was reviewed by the HED-CPRC on May 18,1994 (memorandum of July 27, 1994 from E. Rinde of the NED CPRC to C. Giles-Parker of RD) and classified as a Category C carcinogen without a q-star. The margin-of-exposure (MOE) approach was selected because there was only very weak (limited) evidence of carcinogenic potential at dose levels not considered to be excessive with significant changes observed only at excessive doses. There was no evidence for genotoxicity. There was a statistically significant increase in liver adenomas, carcinomas, and combined liver adenomas and carcinomas in both sexes at doses of 2500 and 4500 ppm. These doses were considered to be excessively high for cancer testing. Liver necrosis and liver adenomas were also noted in males at 300 ppm. There were no statistically significant increases in liver tumors at 10 or 30 ppm. Adequacy of the Dose Levels Tested: The Health Effects Division Cancer Peer Review Committee considered the doses adequate and the study acceptable.

870.4200b Carcinogenicity (feeding) – Rat MRIDs 42090019/ -20

CGA 169374 was administered in the diet to male and female rats [80/sex/dose] for 104 weeks at 0; 10; 20; 500; and 2500 ppm. There were reductions in cumulative body weight gains in the 500 and the 2500 ppm groups. Mean liver weight was increased at week 53 and t termination in the 2500 ppm group . Hepatocellular hypertrophy was observed in the 500 and the 2500 ppm animals at termination. Additional findings in the clinical chemistry data also indicated that liver was the primary target organ for toxicity. No treatment related increased incidences of neoplastic findings were observed in this study. The NOAEL for the study was 20 ppm which was equal to 0.96 and 127 mg/kg/d for males and females respectively. The LOAEL was 500 ppm equal to 24.12 and 32.79 mg/kg/day for males and females respectively based on cumulative decreases in body weight gains. Discussion of Tumor Data No treatment related increased incidences of neoplastic findings were observed in this study. Adequacy of the Dose Levels Tested The dose levels tested were considered adequate by the Cancer Peer Review Committee. (memorandum of July 27,1994 from B. Rinde of the Health Effects Division)

A.4.6 Mutagenicity

Gene Mutation

Guideline # 870.5100 Bacterial assay 42090019, 42710010 Minimum/ guideline	Not mutagenic
Guideline #870.5300, In vitro mammalian cell gene mutation test MRID 42090024 Unacceptable Guideline	No conclusion can be reached from the three nonactivated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.

Cytogenetics

Guideline # 870.5375, Clastogenicity in mammalian cells MRID 46950319, 46950321 Acceptable Guideline MRID 46950323 Guideline #870.5395 Micronucleus test in bone marrow MRID 41710011 Acceptable Guideline Guideline #870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture 4210012 (1992) Acceptable/ guideline	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix. There was no evidence of structural chromosomal aberrations induced over background.Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-169374 (91.2% a.i). CGA-169374 tech. (92.2% a.i.) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.

A.4.7 Neurotoxicity

870.6100 Delayed Neurotoxicity Study – Hen - NA

870.6200 Acute Neurotoxicity Screening Battery – Rat MRID 46950327

In an acute neurotoxicity study (MRID 46950327), groups of fasted Alpk:APfSD Wistar-derived rats (10/sex/dose), at least 42 days old, were given a single oral dose of difenoconazole technical (CGA169374) (94.3% w/w, batch/lot # WM806228) in 1% w/v aqueous carboxymethylcellulose (CMC) at doses of 0, 25, 200, or 2000 mg/kg bw and observed for 14 days. Dose levels selected for this study were based on the results of preliminary acute neurotoxicity study (MRID 46950325). Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on 10 animals/sex/group on days -7, 1, 8, and 15. Body weight and food consumption were measured weekly throughout the study. At study termination, 5 animals/sex/group were euthanized and perfused in situ for neuropathological examination; brain weight was recorded from these animals. Of the perfused animals, 5 animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no unscheduled deaths at any dose level. Weight change on the day of dosing by the control, low-, mid-, and high-dose groups was -2.1, - 1.0, -7.8, and -18.3 g, respectively, for males and 0.0, 2.1, -3.8, and -13.0 g, respectively, for females. Body weight for females had recovered to control levels by day 8. Food consumption for males given 2000 mg/kg was approximately 20% less than control during week 1 only ($p<0.01$). Food consumption for these animals recovered to control levels during week 2. There were no differences from control for females at any dose level or for males at the lower dose levels. These effects on body weight and food consumption were not toxicologically significant.

At 2000 mg/kg, a number of adverse clinical signs were observed on day I (at the time of **peak** effect), including: upward curvature of the spine (8 males, 9 females); tip-toe gait (3, 8);

decreased activity (6, 7); piloerection (3, 5); sides pinched in (3, 7); and subdued (1, 0). Females were affected more than males. All treatment-related clinical signs observed on day 1 showed complete recovery by day 5 (males) or day 7 (females).
Significant decreases in fore-limb grip strength were seen in mid- (23%) and high-dose (26%) males on day 1. Females dosed with 2000 mg/kg had lower motor activities on day 1 (37%), at the time of peak effect, and on day 8 (31%). Males dosed with 200 or 2000 mg/kg had higher motor activities than the controls on day 1, 50% and 55%, respectively, at the time of peak effect. There were no effects on brain weight at any dose level. Neuropathological examination of the central and peripheral nervous system showed no effects of treatment at doses of 2000 mg/kg in both sexes. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in male rats is 200 mg/kg bw based on reduced fore-limb grip strength in males on day 1. The NOAEL is 25 mg/kg bw. The LOAEL for acute neurotoxicity of difenoconazole technical (CGA169374) in female rats is 2000 mg/kg. Based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in, and decreased motor activity. The NOAEL is 200 mg/kg bw.

870.6200 Subchronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID 46950329) difenoconazole technical (94.5% w/w, batch no. WM806228) was administered to groups of 12 male and 12 female Alpk:AP_fSD (Wistar-derived) rats at concentrations of 0, 40, 250, or 1500 ppm in the diet for 90 days. Respective dose levels corresponded to 0, 2.8, 17.3 or 107.0 mg/kg bw/day for males and 0, 3.2, 19.5, or 120.2 mg/kg bw/day for females. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group pretest and during weeks 2, 5, 9, and 14. Cholinesterase activity was not determined. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5/sex from the control group and 5/sex from the 1500 ppm group were subjected to histopathological evaluation of brain and peripheral nervous system tissues. Treatment with difenoconazole at concentrations up to 1500 ppm in the diet had no effect on mortality or clinical signs. Relative to respective control weight, final body weight of males and females in the 1500 ppm group was reduced by 9% and 7%. Body weight gain was reduced by 22% in males and 23% in females. Food consumption was reduced in this group (statistically significant only in females [7%]), and food efficiency was significantly reduced in males by 21% ($p \leq 0.05$) and in females by 21% (ns). Lower dose groups were unaffected. Absolute liver weight in males and females in the 1500 ppm group was increased over respective control weight by 38% and 45%. Liver was not weighed in lower dose groups. The increase in liver weight was considered a normal response to chemical treatment.

During weeks 2, 9 and 14, hind-limb grip strength in males in the 1500 ppm group was reduced by 18 to 27% relative to the control values. At week 14, hind-limb grip strength in males in the 250 ppm group was significantly ($p \leq 0.05$) reduced by 20% relative to the control values. FOB observations in females were unaffected by treatment. Motor activity was unaffected in both sexes at all observation times. Brain weight was unaffected by treatment and there were no treatment-related neuropathological lesions.

The LOAEL in male rats is 250 ppm in the diet (17.3 mg/kg bw/day), based on decreased hind

limb strength. The NOAEL is 40 ppm (2.8 mg/kg bw/day). The LOAEL in female rats is 1500 ppm in the diet (120.2 mg/kg bw/day), based on decreased body weight, body weight gain and food efficiency. The NOAEL is 250 ppm (19.5 mg/kg bw/day). The study is classified as Acceptable/Guideline

A.4.8 Metabolism

870.7485 Metabolism – Rat

Study 1

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in groups of male and, female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [^{14}C] difenoconazole or 0.5 mg/kg unlabeled difenoconazole by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [^{14}C] difenoconazole on day 15. The test compound was labeled with [^{14}C] at either the phenyl or triazole ring.

[^{14}C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. the extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours for an dosing group. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days postexposure.

The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excrete. Three major metabolites were identified in the feces (i.e. metabolites A, B, and C). Two of the metabolites were separated into isomers (i.e., Al, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

These study results indicate that distribution, metabolism, and elimination of difenoconazole were not sex related. There was a slight dose-related difference in the metabolism and elimination difenoconazole. In phenyl- and triazole-labeling studies, fecal excretion of radioactivity was higher in the high-dose animals compared to the low-dose animals, and an additional metabolite was found in the feces of the high-dose animals compared to the low-dose animals. There were no major differences in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some different metabolites

identified. The studies also showed that administration of 0.5 and 100 mg/kg difenoconazole did not induce any apparent treatment-related clinical effects.

The study is classified as acceptable guideline when considered together with data provided in additional rat metabolism studies (MRIDs 42710014, 42710013) submitted as supplemental to this study. This study may be upgraded if the following additional information is provided and is judged to be acceptable:

Study 2

These studies (MRIDs 42710014, 42710013) were submitted because EPA requested additional information not provided in the Sponsor's previously submitted metabolism studies (MRID Nos. 420900-28/29/30/31). The present studies describe the absorption, distribution, and excretion, as well as pharmacokinetics, of [^{14}C] difenoconazole after a single oral gavage dose of 0.5 or 300 mg/kg in rats (Report 1) and isolated and identified urinary metabolites in three females after a single oral gavage dose of 300 mg/kg (Report 2).

Following oral administration of 0.5 or 300 mg/kg ^{14}C-CCA 169374 in rats, the test compound was adequately absorbed and mainly eliminated via the bile; no evidence of bioaccumulation in any tissue was noted. After 48 hours, total recovery (independent of dose and sex) was ≈ 96% of the administered dose. Biliary excretion constituted the main route of elimination with some dose- and sex-dependency (≈ 75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In the urine, 9-14% was eliminated at the low dose versus 1% in the high-dose rats. In the feces, 2-4% was eliminated at the low dose versus 17-22% at the high dose. In cannulated males after 48 hours, ≈ 80% was eliminated via the bile, while ≈ 4% and ≈ 14% were eliminated via urine and feces, respectively. Therefore, this study indicates that most of the dose following oral administration is absorbed as indicated by the biliary excretion data. The dose-related difference in elimination suggests that saturation is reached at the higher dose level resulting in an increase of unabsorbed test material.

Maximum concentration in blood was reached within 2 hours at the low dose and 4 hours at the high dose. By 24 hours, <0.05 ppm equivalent was detected in the blood. Total recovery ranged from 95% to 97% after 48 hours, irrespective of dose and sex. During the first 12 hours, slight differences were evident between males and females with regard to Tmax, Cmax, and rate of elimination. The concentration in females was approximately half of that in males and was eliminated faster than in males. Mean half-lives in males and females from Tmax to 12 hours, were 6.2 and 4.4 hours, respectively; from 24 to 168 hours, they were 2.8 and 3.7 days, respectively.

Following administration of 300 mg/kg of (^{14}C-phenyl) CGA 169374, 3 major urinary metabolites were identified: sulfate conjugates (and their isomers) of HO-CGA 205375, isomers of HO-CGA 205375, and the hydroxyacetic metabolite of H0-CGA 205373. The major urinary metabolites of CGA 169374 have been identified and no single unknown metabolite accounted for >1.1% of the dose.

These studies alone do not meet the minimum requirements for Guidelines 85-1. However, these

studies combined with previously submitted studies (MRID Nos. 420900-28/29/30/31) are considered to be acceptable,

A.4.9 Immunotoxicity

870.7800 Immunotoxicity – Rat

A proposal for difenoconazole immunotoxicity testing regarding dose and species selection to fulfill the 870.7800 guideline requirement has been submitted by the registrant and reviewed by HED (J. Kidwell, 10/20/10, TXR 0055515).

A.4.1 Dermal Toxicity

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

December 18, 2008

MEMORANDUM

SUBJECT: **Difenoconazole - with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.**

PC Code: 128847 **DB Bar Code:** NA

FROM: Jonathan Chen, Ph.D., Senior Toxicologist Jonathan Chen 12/18/08
Jenny Tao, M.D. Senior Toxicologist 12/18/08
Risk Assessment and Science Support Branch (RASSB)
Antimicrobial Division (7510P)

TO: Marshall Swindell
Product Manager, Team #33
Regulatory Management Branch I / AD

THROUGH: Norman Cook, Branch Chief 12/18/08
RSSB/AD (7510P)

Synonym: 1-{2-{4-(4-Chlorophenoxy)-2-chlorophenyl}-4-methyl-1,3-dioxolan-2-ylmethyl}-1H-1,2,4-triazole, CGA169374

Formulation: **Difeno-Shield™**

Active Ingredient:

Difenoconazole .....32.8% a..i.

The technical ingredient has a purity of >99% a.i.

1

Applicant: Syngenta Crop Protection, Inc., Greensboro, N.C. 37419

Use: Difeno-Shield is fungistatic agent that controls and/or inhibits the growth of many fungi associated with odor, staining and discoloration. Difeno-Shield can be applied to paper, wallboard, paint, coatings, caulks, sealants, adhesives, textiles and plastic. It provides an invisible barrier to inhibit the fungal organisms associated with mold and mildew that cause odor staining and discoloration. Difeno-Shield is not intended to protect users or others against food-borne or disease causing organisms. Difeno-Shield is not for use in food or feed handling areas.

Background and Conclusion:

On October 9, 2008, there is AD Toxicity Endpoint Selection Committee special working group meeting held been held to address the appropriate way to use the *in vitro* study results. Attached is the meeting minute.

There are four Difenoconazole dermal absorption studies.
In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

The working group considers both available in vivo and in vitro dermal absorption studies, and an estimated Dermal Absorption factor of 6.0 % was decided to be used in future risk assessment.

Special Working group Meeting
AD Toxicity Endpoint Selection Committee
Potomac Yard, Room S-8621

Meeting Minutes
October 9, 2008

Attendees

Stephen Dapson ..... HED
Pv Shah ..... RD
John Redden ..... RD
Jonathan Chen ..... AD
Jenny Tao ..... AD
Michelle Centra ..... AD

This special working group of the AD Toxicity Endpoint Selection Committee (ADTC) is organized to discuss following Issues:

- The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.
- Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

Jonathan Chen chaired this meeting.

Issue One: The current Office of Pesticide (OPP)'s position in handling the information generated with in vitro dermal absorption studies.

Jonathan Chen points out in creosote RED risk assessment Agency already used an approach of comparing the in vitro studies (Rat skin vs. human skin), calculated an adjustment factor, and applied to the dermal absorption factor selected from in vivo study. Both Pv Shah and Steve Dapson indicate North American Free Trade Agreement (NAFTA) did prepare a draft dermal absorption group position paper on using the in vitro dermal absorption data in risk assessment . In the draft documents, major points are listed below:

1. use of in vitro data as the sole basis for derivation of a Dermal Absorption Factor (DAF) for human health risk assessment is not recommended;
2. Under the situation when both in vitro studies (human and animal) studies and an in vivo animal study are available, the vitro data may be used to extrapolate to human equivalent DAFs for risk assessment.
3. Under this approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. The relationship can be demonstrated as following formula.

IF	$\frac{\text{Animal } \textit{in vitro}}{\text{Animal } \textit{in vivo}} \approx 1$	THEN	Human *in vitro* ≈ Human DAF

Working Group Conclusion:

- Although the NAFTA's position paper is not finalized yet, PV indicated both Health Canada's Pest Management Regulatory Agency (PMRA) and HED management approved this approach. AD should consider it is an appropriate approach in using the in vitro study information;
- The approach should be evaluated on a case-by-case base; and
- In the case when the data set consisting of a "Triple Pack" of in vitro human and animal studies and an in vivo animal study conducted using identical test material can be used to extrapolate human DAF for risk assessment, using following formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

Where

$$\textbf{Adjustment Factor} = \frac{\textbf{Human in vitro DAF}}{\textbf{Animal in vitro DAF}}$$

Note: After the meeting, Steve Dapson sends the most recent NFTA's Draft to the group (See Attachment 1).

Issue Two: Using difenoconazole as an example, with both available in vivo and in vitro dermal absorption studies, select an appropriate dermal absorption factor to be used for risk assessment.

For difenoconazole, there are four dermal absorption studies.

In vivo Dermal Penetration in the Rat, MRID: 47453201
In vivo Dermal Penetration in the Rat, MRID: 46950333
In vitro Absorption through Human Epidermis; MRID: 47453202
In vitro Absorption through Rat Epidermis; MRID: 47453203

Four Different Steps are taken in determine the proposed DAF

Step 1. Determine the appropriate dermal absorption factor based on *in vivo* dermal absorption studies.

There are two *in vivo* dermal absorption studies. The executive summary of these two studies are listed below.

***In vivo* Study 1:**
Roberts, K. and Jones, B. (2007). Difenoconazole technical in vivo dermal penetration study in the rat. Central Toxicology Laboratory, Cheshire, UK. Report Number UR0908-REG, February 6, 2007. MRID 47453201. Unpublished.

In the dermal penetration study (MRID 47453201), Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the skin (10 cm^2) of male Han Wistar rats (16 rats/dose).

Sample doses were prepared by the Sponsor (0.5% carboxy-methylcellulose (CMC) used as vehicle) and applied at a rate of 10 $\mu L/cm^2$ as an aqueous dilution of the concentrate 1/100 (1 mg a.i./mL) or 1/10 (10 mg a.i./mL), aqueous dilutions of the concentrate or as a concentrate (100 mg a.i./mL), corresponding to applied nominal doses of 10, 100, or 1000 $\mu g/cm^2$, respectively.

Exposure duration was 10 hours after application and animals were monitored up to 72 hours post-dosing. Subgroups of rats (4/dose) were terminated at 10, 24, 48, and 72 hours post-dosing. Skin washings, application site materials, excreta, selected tissues, blood and animal carcasses were analyzed for radioactivity.

The majority of the applied doses (80-92%) remained on the skin surface and was readily removed with mild washing indicating that aqueous solutions of [^{14}C]-difenoconazole are poorly absorbed through rat skin. Absorption of [^{14}C]-difenoconazole, though minimal, generally, increased over time for all applied dose concentrations.

Mean Combined Absorption values of [^{14}C]-difenoconazole from the 0.1% (1 mg/ml/10 ug/cm^2) dose was 11.3%, 13.8%, and 13.0% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 1% (10 mg/ml/100 ug/cm^2) dose was 4.1%, 4.3%, and 5.3% at 10, 24, and 72 hours, respectively. Mean Combined Absorption values of [^{14}C]-difenoconazole from the 10% (100 mg/ml, concentrate/1000 ug/cm^2) dose was 1.4%, 2.4%, and 2.8% at 10, 24, and 72 hours, respectively.

For this study, the working group decides a dermal absorption factor of 13.8% (0.1% , 24 hours after exposure) should be the appropriate dermal absorption factor.

***In vivo* Study 2:**
Hassler, S. (2003). Difenoconazole 250 EC (A7402G): Dermal absorption of [Triazole-U-14C] CGA 169374 formulated as Score® 250 EC (A-7402G) in the rat (in vivo). Syngenta Crop Protection AG, CH-4002 Basel, Switzerland. Report Number 051AM-1, May 6, 2003. MRID 46950333. Unpublished.

In the *in vivo* dermal penetration study (MRID 46950333), [Triazole-U-^{14}C] CGA 169374 formulated as SCORE® 250 EC (Batch No. ILA 50.2-1, ILA 50.2-2 (radiolabeled, >98%a.i.)

and AMS 255/3 (non-radiolabeled, >98%a.i.) was applied to the skin (10 µL/cm^2) of 4 male HanBrl: WIST (SPF) rats/dose/treatment at three dose levels: 0.5 (P1), 13 (P2), 2.5µg/cm^2 (P3 and P3a). The results of the high dose level (Group P3) showed a high variability in the efficiency of the washing procedure which did not allow for reliable evaluation of dermal absorption; therefore the high-dose dermal application was repeated and assigned as Group P3a. The nominal exposure duration was 6 hours, at which time the dermal absorption of the test substance was determined. The amount remaining in/on the skin at the application site after washing was determined at three additional time points 24, 48, or 72 hours after application in order to estimate the depletion of the dose. Urine, feces, and blood were collected. The applied concentrations of the low and medium dosages were intended to approximate realistic concentrations recommended for use in the field, whereas the high dose was undiluted product.

Recoveries of the applied doses were 95-104%. The **Total Mean Combined Absorbed Dose** (%) over a specific time period was calculated as exposed skin site (skin strips and remaining treated skin) plus excreta (urine, feces, and cage wash), carcass (all organs), and blood had conflicting results across the doses. After the 6 hour exposure 27, 13, and 9% of the dose was totally absorbed (skin, whole blood, g.i. tract, remaining carcass, feces urine) in the low, mid-, and high-dose group, respectively. At 24 hours, after exposure 6 hour of low, mid- and high dose groups would be 48, 19 and 8 % of the total absorbed dose.

However there was a high level of variation between individual animals in the same dose group. The low and mid-dosed animals show an increase in absorbed dose from 6 to 24 hours and a slight decrease at 48 and 72 hours. However, the high-dose group did not show an increase from 6 until 48 hours with a substantial decrease in radioactivity at 72 hours. The majority of the absorbed radioactivity was isolated in the gastrointestinal tract or carcass at 6 and 24 hour, with increasing amounts found in the feces at 48 and 72 hours. Blood residues during and after dermal exposure at all doses were mostly at or below the limit of detection, the highest blood residues levels were reached between 6 and 8 hours after administration, accounting for 0.01 ppm and 0.25 ppm CGA 168374 equivalents for the middle and high dose levels, respectively. The majority of the radioactivity was washed off and the rinsate was analyzed as CGA 169374 equivalents.

For this study, the working group decides a dermal absorption factor of 48 % (0.5 µg/cm^2 , 24 hours after exposure) should be the appropriate dermal absorption factor.

In conclusion, the working group decides a dermal absorption factor of 48 % should be the appropriate dermal absorption factor based on the *in vivo* dermal absorption studies (MRIDs 47453201 and 46950333).

Step 2. Determine the appropriateness of the in *in vitro* dermal absorption studies.

There are two *in vitro* dermal absorption studies: *in vitro* Absorption through human epidermis (MRID: 47453202) and *in vitro* absorption through rat epidermis (MRID: 47453203). Working group concluded that in the calculation of the dermal absorption, the percent dermal absorption should include the chemical concentration absorbed in the epidermis and amount in receptor fluid. The two studies are summarized below.

***In vitro* Study 1:**

Gledhill, A. (2007). Difenoconazole technical: In vitro absorption through rat epidermis final report. Report Number JV1923-REG0R2, June 28, 2007. MRID 47453203. Unpublished.

In a dermal penetration study (MRID 47453203) Difenoconazole (99.1% a.i.) and [^{14}C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4) was applied to the epidermal membranes of male rats of the Wistar Crl: (WI)BR strain at a rate of 10 µL/cm2 as preparations representing an 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

For the 10-hour exposure period, the percent dermal absorbed are 26%, 2.8% and 2.9 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. For the 24-hour exposure period, the percent dermal absorbed are 40%, 17% and 3.3 % of the applied dose of 10, 100, or 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 1.

Table 1 Summarize the Difenoconazole in each matrix at 24 hours post-application from in vitro Rat dermal absorption study (Gledhill, 2007, MRID 47453203)

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Percent of Applied Does (mean ± SEM)		
	1000 µg/cm^2 (n=5)	100 µg/cm^2 (n=6)	10 µg/cm^2 (n=5)
Donor chamber	0.21 ± 0.19	0.40 ± 0.30	0.29 ± 0.14
Skin wash	98.7 ± 1.58	73.9 ± 3.97	52.8 ± 3.35
Epidermis	2.37 ± 0.67	14.8 ± 2.01	2.51 ± 0.51
Amount in receptor fluid	0.91 ± 0.25	3.67 ± 0.63	37.1 ± 2.55
Total Recovery	102 ± 1.52	93.1 ± 5.82	92.7 ± 1.13
Percent dermal Absorption [1]	3.3%	17%	40%

Note: 1. Percent Dermal Absorption = the total Amount of difenoconazole in epidermis and amount in receptor fluid.

In vitro Study 2:

Davies, D. (2007). *In Vitro* absorption through human epidermis final report. Central Toxicology Laboratory, Cheshire,UK. Report Number JV1922-REG-R1, January 26, 2007. MRID 47453202. Unpublished.

In a dermal absorption study (MRID 47453202), Difenoconazole (99.1% a.i.) and [14C] Difenoconazole (>98% a.i. radiochemical purity, Batch reference: AMS 255/4), was administered to human epidermal membranes at a rate of 10 µL/cm2 as preparations representing a 10, 100, or 1000 µg/cm2. Exposure duration was 10 or 24 hour periods, during which receptor fluid was sampled at specific time intervals. Any difenoconazole remaining on the skin after the two exposure periods was removed by washing.

The applications in this study were designed to simulate potential human dermal exposure arising from the normal use of this type of formulation. The distribution of difenoconazole absorption in the skin was determined for 10 and 24 hours, and a 24 hour absorption profile (µg/cm2/h) was determined. At 10 hours, absorption was 3.46%, 1.15%, and 0.44% for 10, 100, and 1000 µg/cm2, respectively. At 24 hours, the absorption was 4.54%, 1.30%, and 0.40% for the 10, 100, and 1000 µg/cm2, respectively. The Study Results for the 24-hours post application is summarized in Table 2.

Table 2. Summary of the Difenoconazole in Each Matrix at 24 hours Post-application from *in vitro* Human Dermal Absorption study (Davis, 2007).

Matrix analyzed	Amount of difenoconazole in each matrix 24 hours post-application		
	Residues in matrix (Mean % of applied dose) [1]		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
Donor chamber	0.02	0.14	0 .17
Skin wash	96.4	81.6	102
Stratum corneum	0.16	0.52	0.50
Remaining epidermis	0.15	0.35	0.70
Amount in receptor fluid	0.09	0.43	3.34
Total Recovery (sum of above)	96.8	83.0	107
Percent dermal Absorption [2]	0.40 %	1.30%	4.54%

Note: 1. Mean of 6 samples/group.
2. Percent Dermal Absorption = The total Amount of difenoconazole in Stratum corneum, remaining epidermis and Amount in receptor fluid.

In the discussion, following limitations in the both of the two *in vitro* studies are identified.

1. After the skin sample is carefully removed from the site, the skin was soaked in 1.5 M sodium bromide for 20 minutes and rinsed after soaking with distilled water, and the epidermis was peeled from the dermis. Working group suggested that it would have better to dermatomed the skin (350-450 micron) rather than chemical separating , should be included in the dermal absorption study; and

2. The epidermis is stored frozen in aluminum foil until it is needed. Although the membrane integrity was determined by measurement of the electrical resistance across the skin membrane: membranes with a measured resistance, working group still consider freezing of the skin sample is not recommended.

However, because limitations of the dermal absorption studies are similar between the *in vitro* rat dermal absorption and the *in vitro* human dermal absorption study, and the *in vitro* rat DAF is equivalent to the rat in vivo DAF. Therefore, working group concluded that the in vitro dermal absorption studies are appropriate to be used to establish DAFs for risk assessment.

Step 3. Identify the appropriate Adjustment Factor for extrapolating from Rat DAF to Human DAF,

Working group decides the 24-hour exposure period is more appropriate in comparing the difference between in vitro rat *vs.* human skin studies. Table 1 summarizes the difenoconazole in each matrix at 24 hours post-application from in vitro rat dermal absorption study (Gledhill, 2007, MRID 47453203). Table 3 summarizes the calculated ratio of in vitro human dermal absorption factor vs. in vitro rat dermal absorption of difenoconazole .

Table 3. Summarize the Calculated Ratio of *in vitro* Human Dermal Absorption Factor (DAF) vs. *in vitro* Rat Dermal Absorption Factor of Difenoconazole .

Calculated DAF	Percent dermal Absorption		
	1000 µg/cm^2	100 µg/cm^2	10 µg/cm^2
In vitro Human DAF [1]	0.40 %	1.30 %	4.54 %
In vitro Animal DAF [2]	3.3 %	17 %	40 %
Ratio	0.12	0.07	0.11

Note: 1. Derived from the summary of the Rat dermal absorption study (Gledhill, 2007, MRID 47453203), Table 1.
2. Derived from the summary of Human Dermal Absorption study ((Davis, 2007, MRID 47453202), Table 2.

Step 4. Calculation of the Estimated Dermal Absorption Factor

The Working group decides data set give the highest ratio should be used as the adjustment factor. Therefore, the dataset derived from 1000 $\mu g/cm^2$ which gave the highest ratio of 0.12 should be used for the derivation of the estimated human dermal absorption factor.

Therefore, based on the formula

Estimated Human DAF = Adjustment Factor x Animal in vivo DAF

$$= 0.12 \times 48\% = 5.76\% \text{ (Ca. 6\%)}$$

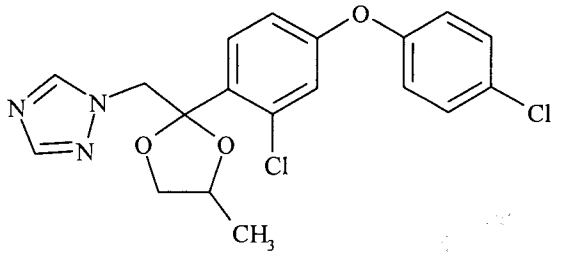
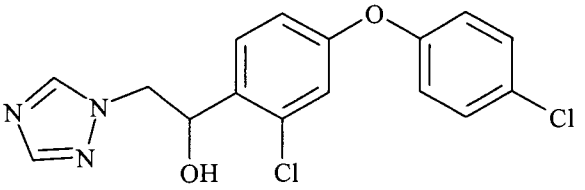
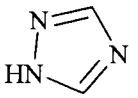
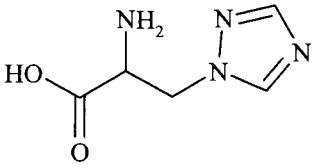
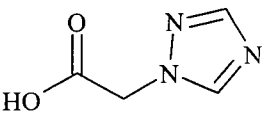
Therefore, a human estimated DAF of ca. 6 % should be used for risk assessment.

Working Group Conclusion:

Considering both available *in vivo* and *in vitro* dermal absorption studies, an estimated Dermal Absorption factor of 6.0 % should be used in future risk assessment.

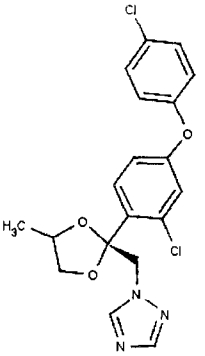
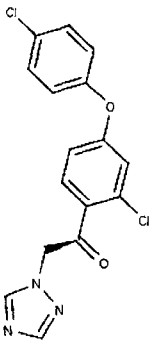
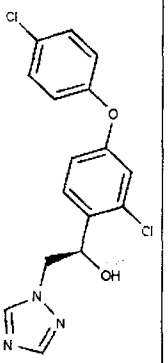
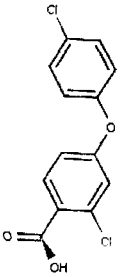
B. METABOLISM

B.1 Chemical Names And Structures

Table B.1 Difenoconazole Nomenclature.	
Chemical structure	
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-({2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl}methyl)-1H-1,2,4-triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole
CAS registry number	119446-68-3
Chemical structure of CGA-205375 livestock metabolite	
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolylalanine (TA)	
Chemical structure of Triazolylacetic acid (TAA)	

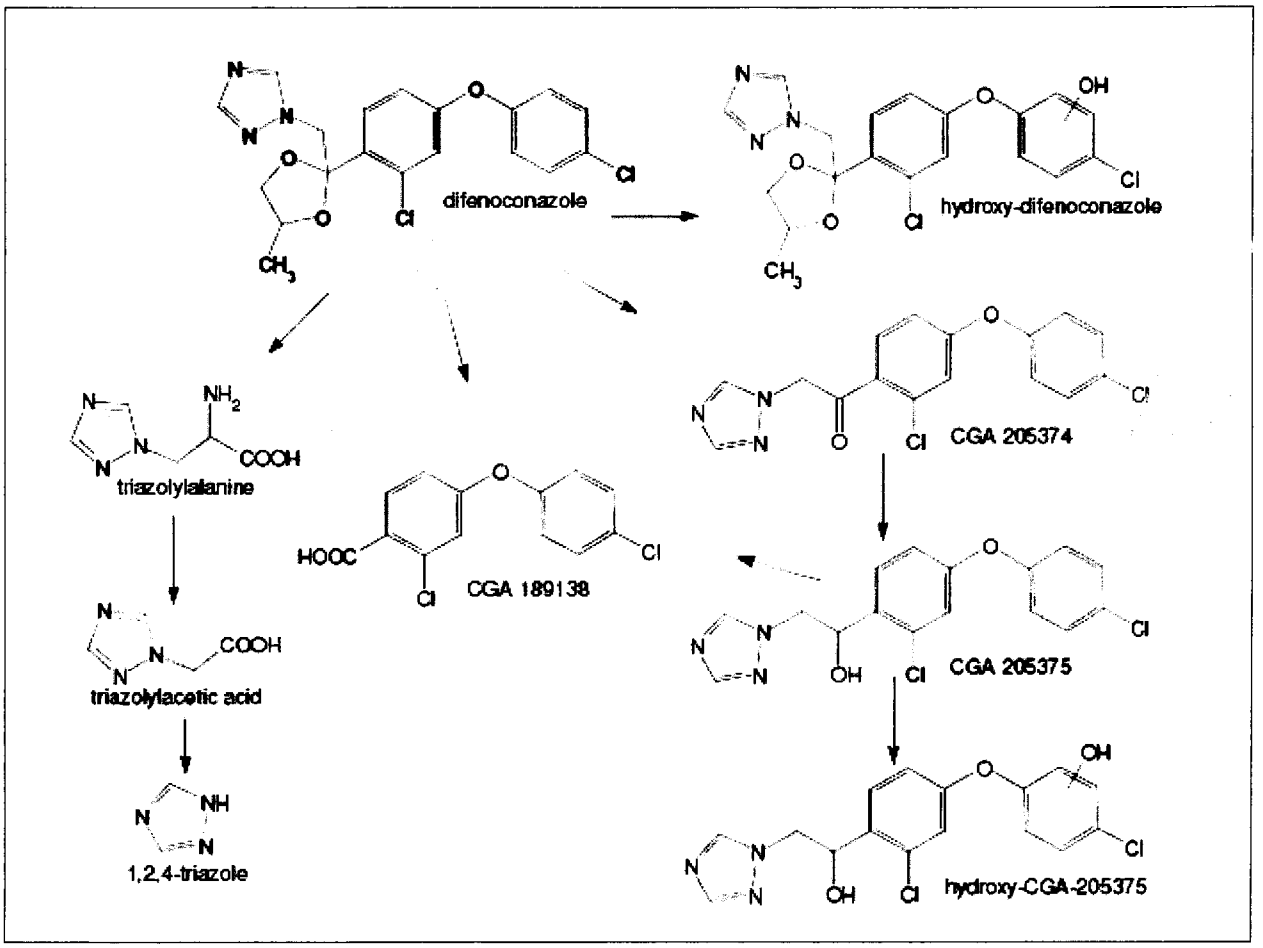
B.2 Metabolism Summary Table

Table B.2 Maximum Residues of CGA-205374, CGA-205375, and CGA-189138 in Metabolism Studies Reflecting Foliar Appls. Note: Excludes data reflecting 0-day PHIs (parent was >85% of TRR) and RACs having no detectable residues of the subject metabolites.

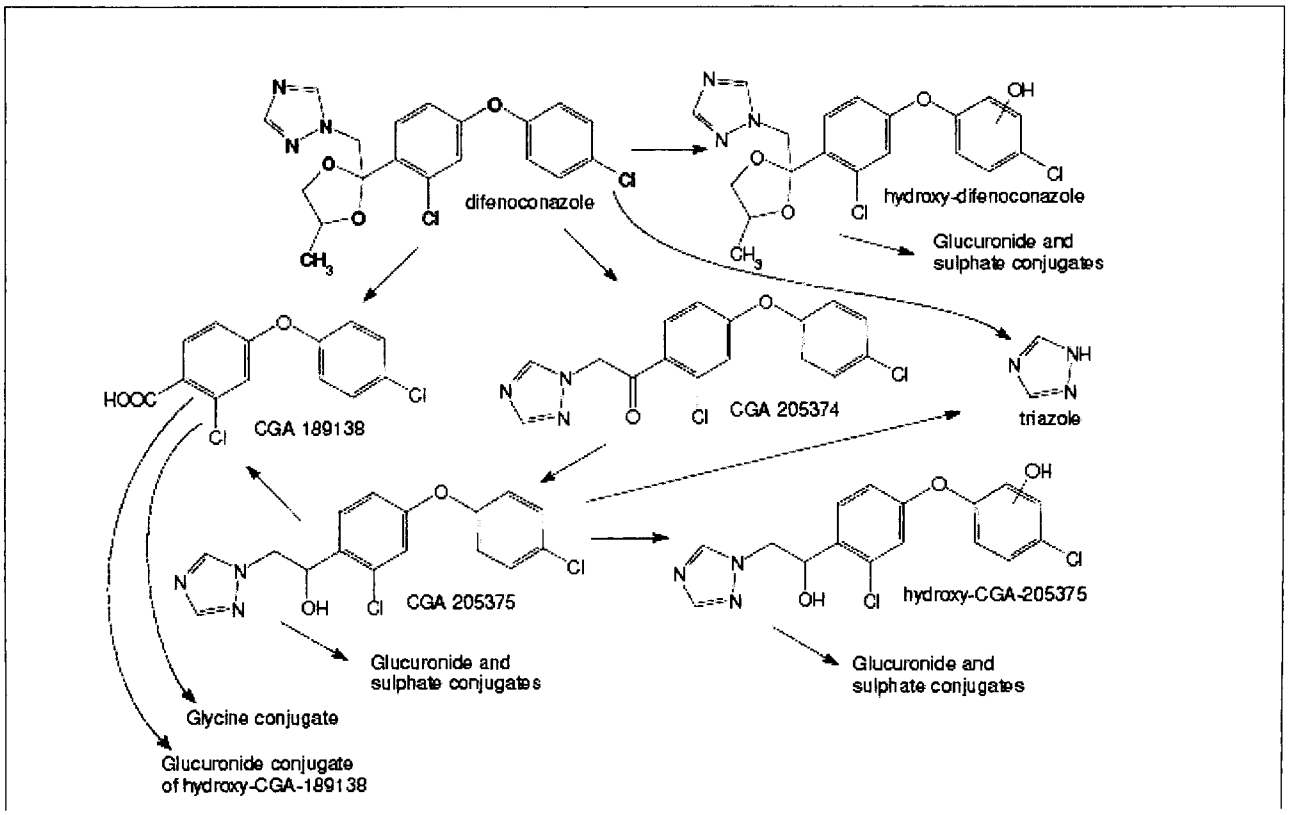
Crop [MRID Citation]	RAC	Radiolabel Position	Number of Appls. Times Rate (lb ai/A)	PHI (days)	Residues Expressed as ppm (% of TRR)			
					Difenoconazole 	CGA-205374 	CGA-205375 	CGA-189138 
Wheat [42090032]	Stalks	^{14}C Phenyl	4 x 0.22	29	23 (50%)	--	--	--
		^{14}C Triazole			27 (50%)	--	2.7 (5%)	--
Canola (Rape seed) [44701701] [44701702]	Stalks	^{14}C Phenyl	2 x 0.11	53	0.745 (17.3%)	--	0.608 (14.1%)[1]	0.069 (1.6%)[2]
		^{14}C Triazole			0.828 (17.1%)	0.058 (1.2%)[2]	0.828 (17.1%)[1]	--
	Pods	^{14}C Phenyl			0.570 (18.1%)[1]	0.009 (0.3%)[2]	0.340 (10.8%)[1]	0.054 (1.7%)[2]
		^{14}C Triazole			0.814 (17.3%)[1]	0.038 (0.8%)[2]	0.612 (13.0%)[1]	--
	Seed	^{14}C Phenyl			0.022 (14.4%)	--	0.012 (7.9%)	0.0004 (0.3%)
		^{14}C Triazole			0.093 (4.1%)	--	0.014 (0.6%)	--
Potato[3] [42090036]	Foliage	^{14}C Phenyl	6 x 0.11	12	9.47 (76.4%)	0.14 (1.1%)	0.27 (2.2%)	0.07 (0.5%)
	Tuber	^{14}C Phenyl			0.001 (8.7%)	0.0004 (3.1%)	0.0004 (3.0%)	--
Tomato [42090035]	Foliage	^{14}C Phenyl	3 x 0.22	40	1.1 (31%)	0.12 (3.4%)		0.18 (5.2%)
		^{14}C Triazole			2.1 (28%)	0.32 (4.3%)		--
		^{14}C Phenyl	2 x 0.22	14	1.3 (59.1%)	0.08 (3.8%)		0.09 (4.3%)
		^{14}C Triazole			1.5 (52.1%)	0.10 (3.5%)		--
Tomato [42090038] [42090039]	Foliage	^{14}C Phenyl	6 x 0.11	35	5.36 (64.7%)	0.32 (3.9%)	0.20 (2.4%)[4]	0.08 (0.9%)
		^{14}C Triazole			5.25 (68.0%)	0.13 (1.63%)	0.76 (9.8%)[5]	--
	Fruit	^{14}C Phenyl			0.11 (66.3%)	0.002 (1.4%)	0.005 (2.6%)[6]	--
		^{14}C Triazole			0.10 (50.9%)	0.001 (0.52%)	0.002 (0.74%)	--
Grape [43673201]	Fruit	^{14}C Phenyl	3 x 0.22	20	0.065 (51.2%)	0.005 (4.1%)	0.008 (6.6%)	0.005 (4.0%)
		^{14}C Triazole	5 x 0.22		0.052 (45.1%)	0.002 (1.7%)	0.004 (3.5%)	--
	Leaves	^{14}C Phenyl	3 x 0.22		4.260 (46.4%)	0.762 (8.3%)	0.395 (4.3%)	0.487 (5.3%)
		^{14}C Triazole	5 x 0.22		1.821 (31.5%)	0.173 (3.0%)	0.225 (3.9%)	--

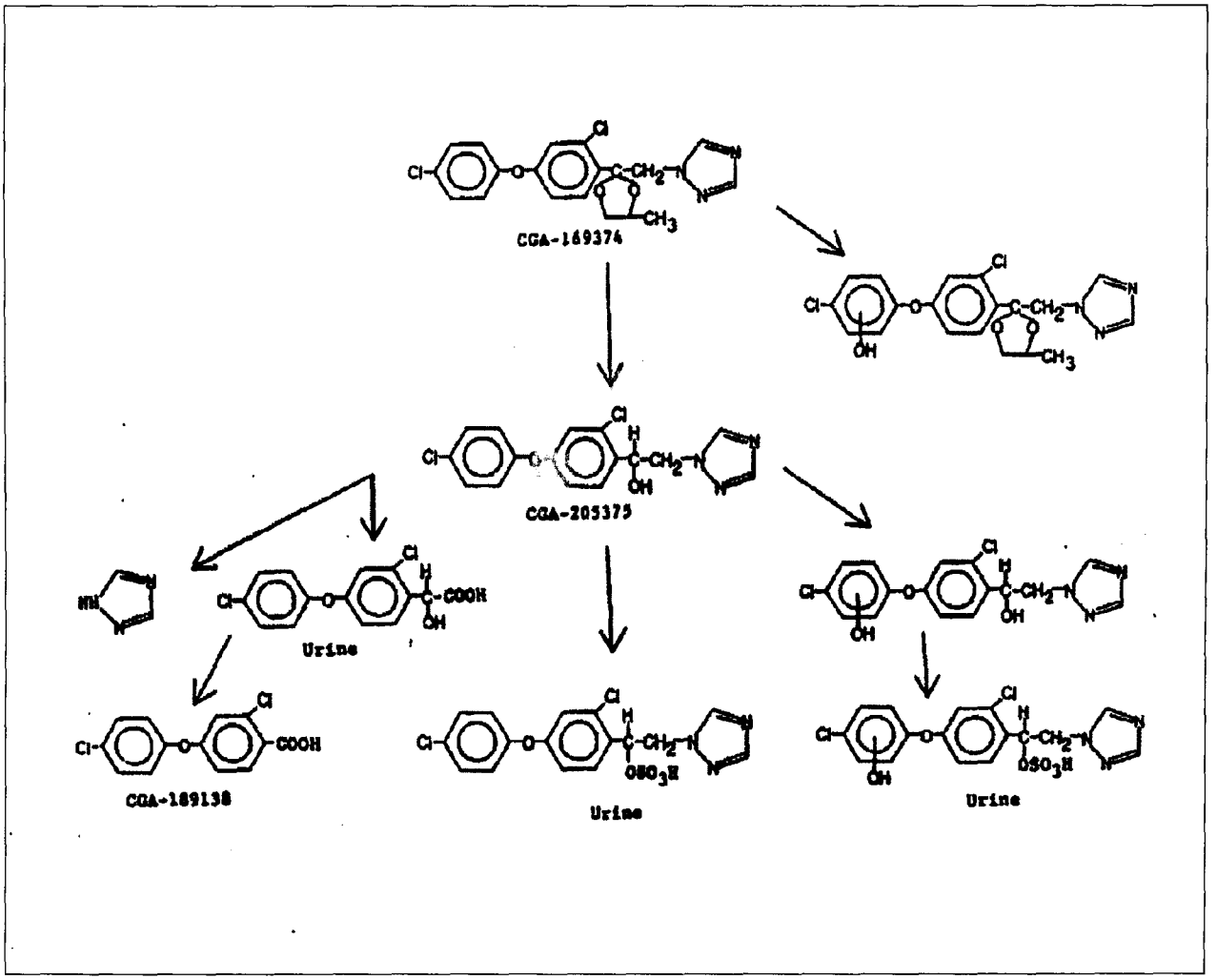
B.3 Metabolic Pathways

Plant

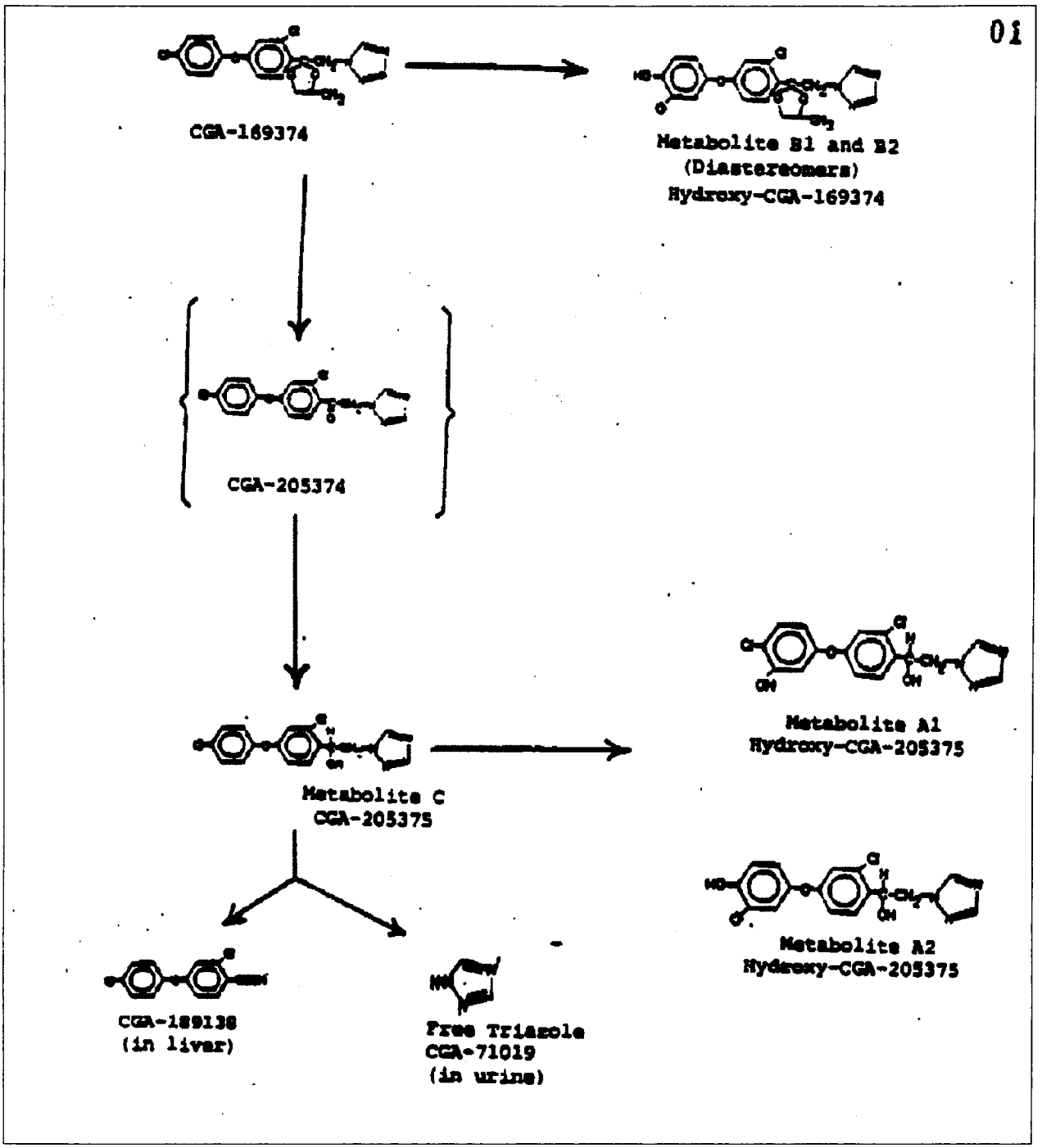


Goat Metabolism

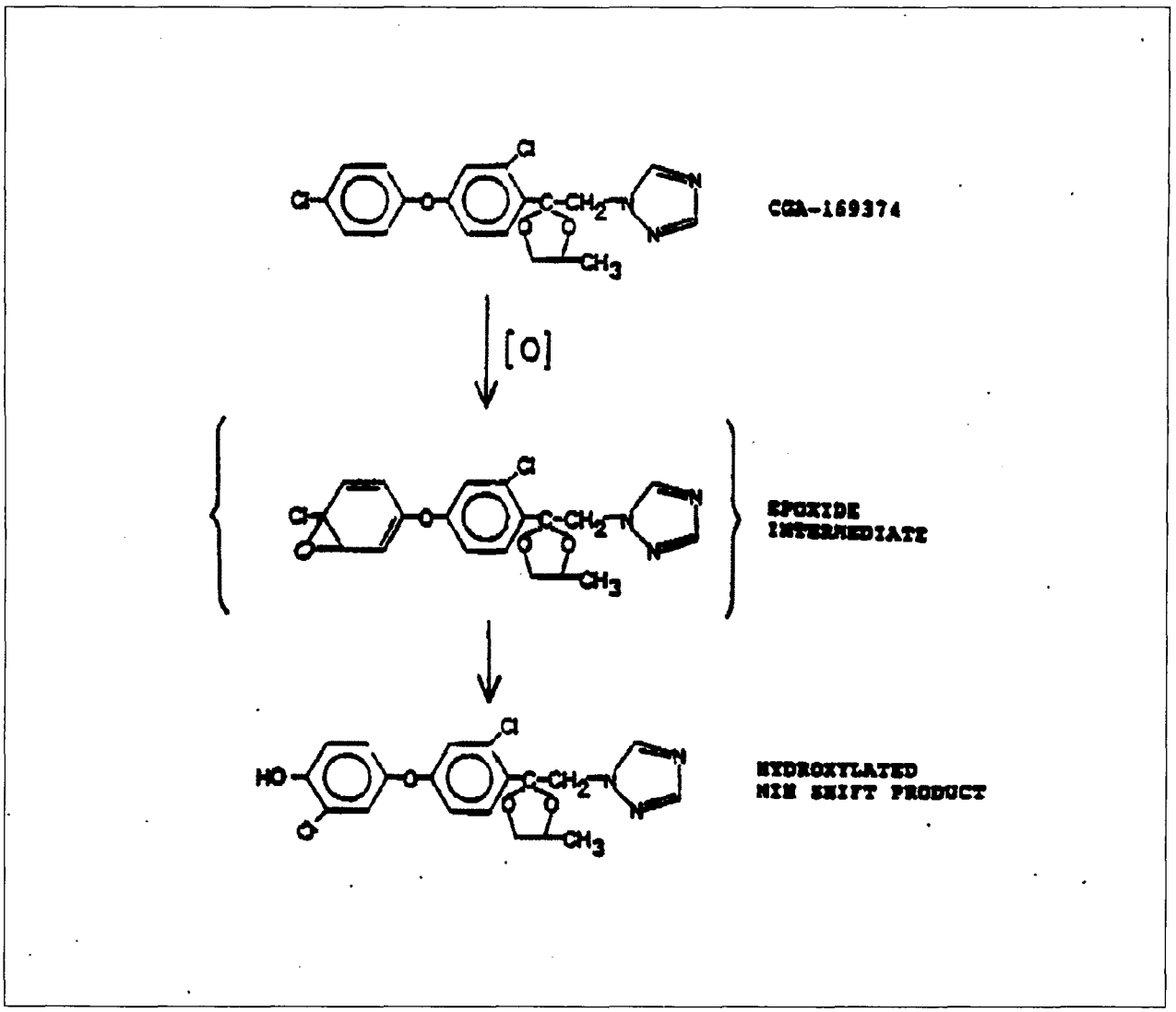




Proposed metabolic pathway in the rat (urine)



Proposed metabolic pathway in rat (feces). The ketone, CGA-205374, is presented as an intermediate from parent to CGA-205375.



Proposed mechanism for formation of metabolites A & B by the NIH Shift

C. PHYSICAL/CHEMICAL PROPERTIES

Table C.1 Physicochemical Properties of Difenoconazole.		
Parameter	**Value**	**Reference**
Melting point	78.6 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 °C (saturated solution)	
Density	1.37 g/cm^3 at 20 °C	
Water solubility	3.3 ppm at 20 °C	
Solvent solubility	g/100 mL at 25 °C: n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10^{-10} mm Hg at 25 °C	
Dissociation constant, pK_a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20°C is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian
Octanol/water partition coefficient, Log(K_{OW})	4.2 at 25 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ_{max} at about 200 and 238 nm (in methanol at 26 °C)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

D. REVIEW OF HUMAN RESEARCH

Klonne, D. (1999) Integrated Report for Evaluation of Potential Exposures to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns: Lab Project Number: OMA005: OMA001: OMA002. Unpublished study prepared by Riceerca, Inc., and Morse Laboratories. 2213 p. (MRID 44972201).

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

13544

R195625

Chemical Name: Difenoconazole

PC Code: 128847
HED File Code: 14000 Risk Reviews
Memo Date: 10/27/2011
File ID: 00000000
Accession #: 000-00-0137

HED Records Reference Center
10/31/2011